Charles H. Chevalier
J. Brugh Lower
Christine A. Gaddis
Rachel S. Johnston
GIBBONS P.C.
One Gateway Center
Newark, NJ 07102-5310
(973) 596-4611
cchevalier@gibbonslaw.com
jlower@gibbonslaw.com
rjohnston@gibbonslaw.com

Attorneys for Plaintiff Amgen Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AMGEN INC., Plaintiff, v. SANDOZ INC., et al., Defendants.	Civil Action No. 18-11026 (MAS)(DEA) (consolidated) Hon. Michael A. Shipp, U.S.D.J. Hon. Douglas E. Arpert, U.S.M.J.

PLAINTIFF AMGEN INC.'S PROPOSED FINDINGS OF FACT

AMGEN'S PROPOSED FINDINGS OF FACT

I. THE PATENTS-IN-SUIT AND THE ASSERTED CLAIMS

A. U.S. Patent No. 7,427,638 (Composition Patent)

1. United States Patent No. 7,427,638 ("the '638 Patent") is entitled, "(+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione, and Methods of Synthesis and Compositions Thereof." JSF ¶ 18 (ECF No. 422).[1]

2. George W. Muller, Peter H. Schafer, Hon-Wah Man, and Chuansheng Ge are the inventors of the '638 Patent. JSF ¶ 20 (ECF No. 422).

3. The '638 Patent issued on September 23, 2008, to Celgene Corporation. JSF ¶ 19 (ECF No. 422).

4. The '638 Patent issued from U.S. Patent Application No. 11/106,142, filed on April 13, 2005. JSF ¶ 22 (ECF No. 422).

5. Amgen is the current assignee of the '638 Patent. JSF ¶ 21 (ECF No. 422).

6. The '638 Patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for Otezla® (NDA No. 205437). JSF ¶ 24 (ECF No. 422).

7. The FDA's Orange Book lists the expiration date of the '638 Patent as February 16, 2028. JSF ¶ 25 (ECF No. 422).

8. Amgen is asserting Claims 3 and 6 of the '638 Patent (the "'638 Patent Asserted Claims") against Sandoz and Zydus in this consolidated action. JSF ¶ 23 (ECF No. 422).

9. Claim 1 of the '638 Patent is an independent claim and recites: "[a] pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a

[1] The parties have jointly submitted errata to the Court Reporter for the Trial Transcripts for June 22, 23, 24, and 25. Amgen expects to provide updated Proposed Findings of Fact with revised citations to the final Trial Transcripts for those dates on July 15, 2021, along with the hyperlinked Post-Trial Brief.

pharmaceutically acceptable salt, solvate, or hydrate, thereof; and a pharmaceutically acceptable carrier, excipient or diluent." JSF ¶ 26 (ECF No. 422).

10. Claim 2 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 1 wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient." JSF ¶ 27 (ECF No. 422).

11. Claim 3 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 2 wherein said pharmaceutical composition is suitable for oral administration to a patient." JSF ¶ 28 (ECF No. 422).

12. Claim 4 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 2 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 1 mg to 1000 mg." JSF ¶ 29 (ECF No. 422).

13. Claim 5 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 4 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 5 mg to 500 mg." JSF ¶ 30 (ECF No. 422).

14. Claim 6 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 5 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 10 mg to 200 mg." JSF ¶ 31 (ECF No. 422).

B. U.S. Patent No. 8,455,536 (Psoriasis Patent)

15. United States Patent No. 8,455,536 ("the '536 Patent") is entitled, "Methods of Using (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione." JSF ¶ 32 (ECF No. 422).

16. George W. Muller, Peter H. Schafer, Hon-Wah Man, and Chuansheng Ge are the inventors of the ’536 Patent. JSF ¶ 34 (ECF No. 422).

17. The ’536 Patent issued on June 4, 2013, to Celgene Corporation. JSF ¶ 33 (ECF No. 422).

18. The ’536 Patent issued from U.S. Patent Application No. 12/630,788, filed on December 3, 2009. JSF ¶ 36 (ECF No. 422).

19. Amgen is the current assignee of the ’536 Patent. JSF ¶ 35 (ECF No. 422).

20. The ’536 Patent is listed in the FDA’s Orange Book for Otezla (NDA No. 205437). JSF ¶ 38 (ECF No. 422).

21. The FDA’s Orange Book lists the expiration date of the ’536 Patent as March 19, 2023. JSF ¶ 39 (ECF No. 422).

22. Amgen is asserting Claim 6 of the ’536 Patent (the “’536 Patent Asserted Claim”) against Sandoz and Zydus in this consolidated action. JSF ¶ 37 (ECF No. 422).

23. Claim 1 of the ’536 Patent is an independent claim and recites: “[a] method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose.” JSF ¶ 40 (ECF No. 422).

24. Claim 6 of the ’536 Patent recites: “[t]he method of claim 1, wherein the stereomerically pure compound comprises greater than about 97% by weight of (+) isomer based on the total weight percent of the compound.” JSF ¶ 41 (ECF No. 422).

C. U.S. Patent No. 7,893,101 (Form B Patent)

25. United States Patent No. 7,893,101 (“the ’101 Patent”) is entitled, “Solid Forms Comprising (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-

Acetylaminoisoindoline-1,3-Dione, Compositions Thereof, and Uses Thereof." JSF ¶ 42 (ECF No. 422).

26. George W. Muller, Peter H. Schafer, Hon-Wah Man, Chuansheng Ge, and Jean Xu are the inventors of the '101 Patent. JSF ¶ 44 (ECF No. 422).

27. The '101 Patent issued on February 21, 2011, to Celgene Corporation. JSF ¶ 43 (ECF No. 422).

28. The '101 Patent issued from U.S. Patent Application No. 12/079,615, filed on March 27, 2008. JSF ¶ 46 (ECF No. 422).

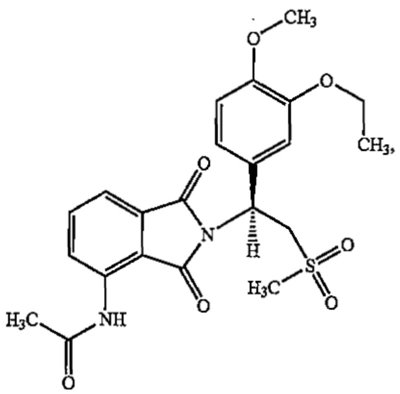
29. Amgen is the current assignee of the '101 Patent. JSF ¶ 45 (ECF No. 422).

30. The '101 Patent is listed in the FDA's Orange Book for Otezla (NDA No. 205437). JSF ¶ 48 (ECF No. 422).

31. The FDA's Orange Book lists the expiration date of the '101 Patent as December 9, 2023. JSF ¶ 49 (ECF No. 422).

32. Amgen is asserting Claims 1 and 15 of the '101 Patent (the "'101 Patent Asserted Claims") against Sandoz and Zydus in this consolidated action. JSF ¶ 47 (ECF No. 422).

33. Claim 1 of the '101 Patent, is an independent claim and recites: "[a] form B crystal form of the compound of Formula (1):



which is enantiomerically pure, and which has an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ." JSF ¶ 50 (ECF No. 422).

34. Claim 15 of the '101 Patent is an independent claim and recites: "[a] solid pharmaceutical composition comprising the crystal form of any one of the claims 1 and 2 to 13." JSF ¶ 51 (ECF No. 422).

D. U.S. Patent No. 8,093,283 (Form A Patent)

35. United States Patent No. 8,093,283 ("the '283 Patent") is entitled, "Solid Forms Comprising (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione, Compositions Thereof, and Uses Thereof." JSF ¶ 52 (ECF No. 422).

36. George W. Muller, Peter H. Schafer, Hon-Wah Man, Chuansheng Ge, and Jean Xu are the inventors of the '283 Patent. JSF ¶ 54 (ECF No. 422).

37. The '283 Patent issued on January 10, 2012, to Celgene Corporation. JSF ¶ 53 (ECF No. 422).

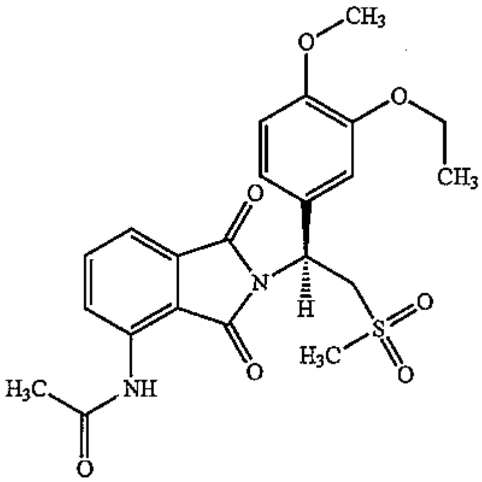
38. The '283 Patent issued from U.S. Patent Application No. 12/945,800, filed on November 12, 2010. JSF ¶ 56 (ECF No. 422).

39. Amgen is the current assignee of the '283 Patent. JSF ¶ 55 (ECF No. 422).

40. The FDA's Orange Book lists the expiration date of the '283 Patent as March 19, 2023. JSF ¶ 58 (ECF No. 422).

41. Amgen is asserting Claims 2 and 27 of the '283 Patent (the "'283 Patent Asserted Claims") against Zydus in this consolidated action. JSF ¶ 57 (ECF No. 422).

42. Claim 1 of the '283 Patent is an independent claim and recites: "[a]n unsolvated crystal form of the compound of Formula (I):



which is enantiomerically pure, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at 8.1, 14.4, 17.4, 23.6 and 25.1 degrees 2θ, or Form F, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 15.6, 17.3, and 25.4 degrees 2θ." JSF ¶ 59 (ECF No. 422).

43. Claim 2 of the '283 Patent recites: "[t]he crystal form of claim 1, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 14.4, 17.4, 23.6, and 25.1 degrees 2θ." JSF ¶ 60 (ECF No. 422).

44. Claim 27 of the '283 Patent is an independent claim and recites: "[a] solid pharmaceutical composition comprising the crystal form of claim 2." JSF ¶ 61 (ECF No. 422).

E. U.S. Patent No. 10,092,541 (Titration Patent)

45. United States Patent No. 10,092,541 ("the '541 Patent") is entitled, "Methods for the Treatment of Diseases Ameliorated by PDE4 Inhibition Using Dosage Titration of Apremilast." JSF ¶ 62 (ECF No. 422).

46. Robert Day is the inventor of the '541 Patent. JSF ¶ 64 (ECF No. 422).

47. The '541 Patent issued on October 9, 2018, to Celgene Corporation. JSF ¶ 63 (ECF No. 422).

48. The effective filing date for the '541 Patent is August 15, 2014. JSF ¶ 66 (ECF No. 422).

49. Amgen is the current assignee of the '541 Patent. JSF ¶ 65 (ECF No. 422).

50. The ’541 Patent is listed in the FDA’s Orange Book for Otezla (NDA No. 205437). JSF ¶ 68 (ECF No. 422).

51. The FDA’s Orange Book lists the expiration date of the ’541 Patent as May 29, 2034. JSF ¶ 69 (ECF No. 422).

52. Amgen is asserting Claims 2, 19, and 21 of the ’541 Patent (the “’541 Patent Asserted Claims”) against Sandoz and Zydus in this consolidated action. JSF ¶ 67 (ECF No. 422).

53. Claim 2 of the ’541 Patent is an independent claim and recites: “[a] method of treating a patient with stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the patient is suffering from psoriasis, the method consisting of: (a) administering to a patient stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in an initial titration dosing schedule consisting of (i) 10 mg in the morning on the first day of administration; (ii) 10 mg in the morning and 10 mg after noon on the second day of administration; (iii) 10 mg in the morning and 20 mg after noon on the third day of administration; (iv) 20 mg in the morning and 20 mg after noon on the fourth day of administration; (v) 20 mg in the morning and 30 mg after noon on the fifth day of administration; and (b) on the sixth and every subsequent day, administering to the patient 30 mg in the morning and 30 mg after noon of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione.” JSF ¶ 70 (ECF No. 422).

54. Claim 19 of the ’541 Patent recites: “[a] method as in any one of claims 1–14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 98% by weight of the (+) isomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-

acetylaminoisoindoline-1,3-dione based on the total weight of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione." JSF ¶ 71 (ECF No. 422).

55. Claim 21 of the '541 Patent recites: "[a] method as in any one of claims 1–14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered in tablet form." JSF ¶ 72 (ECF No. 422).

II. THE PARTIES

56. Plaintiff Amgen Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at One Amgen Center Drive, Thousand Oaks, California 91320. JSF ¶ 1 (ECF No. 422).

57. Defendant Sandoz Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 100 College Road West, Princeton, New Jersey 08540. JSF ¶ 7 (ECF No. 422).

58. Defendant Zydus Pharmaceuticals (USA) Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 73 Route 31 North, Pennington, New Jersey 08534. JSF ¶ 8 (ECF No. 422).

59. Civil Action Nos. 18-11269, 18-11026, and 19-18806 have been consolidated for all purposes, including discovery, case management, and trial under the lead case docket number 18-11026 (hereinafter "Consolidated Actions"), and a proposed trial consolidation order has been filed. JSF ¶ 9 (ECF No. 422).

III. THE PRODUCTS AT ISSUE

A. Otezla NDA No. 205437

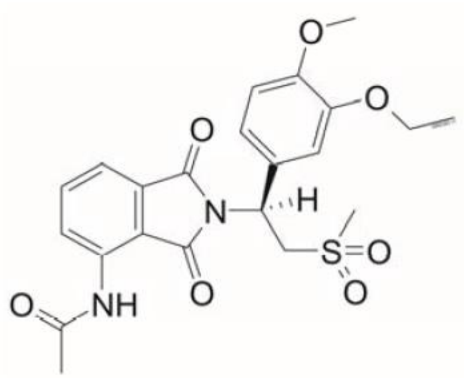
60. Amgen holds approved New Drug Application ("NDA") No. 205437 for 10 mg, 20 mg, and 30 mg, oral apremilast tablets, which are sold in the United States under the trademark OTEZLA®. JSF ¶ 10 (ECF No. 422).

61. Otezla tablets are FDA-approved to treat adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, adult patients with active psoriatic arthritis, and adult patients with oral ulcers associated with Behçet's Disease. *See* JTX-110 at JTX-110_1.

62. About 3 percent of the U.S. population has plaque psoriasis. Trial Tr. at 277:18–21 (Alexis Direct 6.15.21). The breakdown of psoriasis between men and women is roughly 50/50 and psoriasis can affect patients of almost any age. Trial Tr. at 296:15–17 (Alexis Direct 6.15.21); 1756:14–25 (Alexis Direct 6.25.21).

63. The active ingredient in Otezla is apremilast. *See* JTX-110 at JTX-110_8.

64. Apremilast can be represented by the chemical name, "(+)2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and the chemical structure shown below:



See JTX-110 at JTX-110_8.

65. Apremilast is a phosphodiesterase type 4 ("PDE4") inhibitor. JTX-110 at JTX-110_8. Apremilast is unique in terms of its mechanism of action: it is a small molecule that gets into the cells in the body and exerts its anti-inflammatory effect and rebalances the immune system by blocking the production of TNFα and other cytokines. Trial Tr. at 168:19–169:2 (Schafer Direct 6.14.21). To date, apremilast is the only PDE4 inhibitor approved to treat psoriasis. Unlike other drugs that are approved for psoriasis, apremilast is not immunosuppressive. Trial Tr. at 169:3–9 (Schafer Direct 6.14.21); 304:13–23 (Alexis Direct 6.15.21).

66. Otezla is an embodiment of claims 3 and 6 of the '638 Patent. JSF ¶ 15 (ECF No. 422).

67. The use of Otezla according to the labeling for Otezla is an embodiment of claim 6 of the '536 Patent. JSF ¶ 16 (ECF No. 422).

68. The "Dosage and Administration" section of the labeling for Otezla recites:

- To reduce the risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg twice daily according to the following schedule (2.1)
    - Day 1: 10 mg in the morning
    - Day 2: 10 mg in the morning and 10 mg in the evening
    - Day 3: 10 mg in the morning and 20 mg in the evening
    - Day 4: 20 mg in the morning and 20 mg in the evening
    - Day 5: 20 mg in the morning and 30 mg in the evening
    - Day 6 and thereafter: 30 mg twice daily"
- Dosage in Severe Renal Impairment:
    - Recommended dose is 30 mg once daily (2.2)
    - For initial dosage titration, titrate using only morning schedule listed in Table 1 and skip afternoon doses (2.2)

See JTX-110 at JTX-110_1.

69. The Orange Book entry for Otezla includes, as is required by law, "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." *See* 21 U.S.C. §355(b)(1).

70. The ’358 Patent was listed in the Orange Book of Otezla. *See* DTX-384 at DTX-384_1000.

71. Claim 1 of the ’358 Patent covers billions of compounds, of which apremilast is one of the billions. Trial Tr. at 598:25–599:4 (Gribble Direct 6.18.21); 664:14–23 (Gribble Cross 6.18.21); 1492:12–16, 1492:22–25 (Davies Redirect 6.23.21). Claim 16 is the only claim in the ’358 Patent that claims specific compounds. Neither Example 12 nor apremilast are claimed in claim 16. The ’358 Patent does not include any specific mention of apremilast. Trial Tr. at 624:23–25 (Gribble Cross 6.18.21). Nor is the chemical structure or chemical name for apremilast explicitly set out in the ’358 Patent. Trial Tr. at 625:1–5, 625:13–16 (Gribble Cross 6.18.21).

B. DEFENDANTS’ PROPOSED GENERIC PRODUCTS

1. Sandoz’s Proposed ANDA Products

72. On March 21, 2018, Sandoz submitted ANDA No. 211658 (the “Sandoz ANDA”) to FDA under 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, offer for sale, and/or sale of apremilast tablets (“Sandoz’s ANDA Products”), a generic version of 10 mg, 20 mg, and 30 mg Amgen’s Otezla products. JSF ¶ 90 (ECF No. 422); SSF (A3) ¶ 1, 4 (ECF No. 422).

73. Sandoz’s ANDA included a Paragraph IV Certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the ’536 Patent, the ’638 Patent, and the ’101 Patent are invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Sandoz’s ANDA Products. JSF ¶ 92 (ECF No. 422); SSF (A3) ¶ 2 (ECF No. 422).

74. Sandoz later amended its ANDA with a Patent Amendment as required under 21 CFR §§ 314.95(b) and 314.95(e) to include a new Paragraph IV Certification asserting that the ’541 Patent is also invalid, unenforceable, or will not be infringed by the manufacture, use,

offer for sale, sale and/or importation of Sandoz's ANDA Products. JSF ¶ 93 (ECF No. 422); SSF (A3) ¶ 3 (ECF No. 422).

75. The Sandoz ANDA references Amgen's NDA No. 205437. JSF ¶ 91 (ECF No. 422).

2. Zydus's Proposed ANDA Products

76. On March 21, 2018, Zydus submitted ANDA No. 211859 (the "Zydus ANDA") to FDA under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of apremilast tablets ("Zydus's ANDA Products"), a generic version of 10 mg, 20 mg, and 30 mg Amgen's Otezla products. JSF ¶ 94; ZSF ¶ 1 (ECF No. 422).

77. Zydus's ANDA included a Paragraph IV Certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '536 Patent, the '638 Patent, and the '101 Patent are invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Zydus's ANDA Products. JSF ¶ 96 (ECF No. 422).

78. Zydus later amended its ANDA with a Patent Amendment as required under 21 CFR § 314.95(b) and 314.95(e) to include a new Paragraph IV Certification asserting that the '541 Patent is also invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Zydus's ANDA Products. JSF ¶ 97 (ECF No. 422).

79. Zydus had actual and constructive notice of the '283 Patent prior to filing Zydus's ANDA, at least because the '283 Patent is in the same patent family as the '536 Patent, the '638 Patent, and the '101 Patent against which Zydus filed its Paragraph IV Certification. JSF ¶ 96 (ECF No. 422); JTX-3; JTX-5; JTX-6.

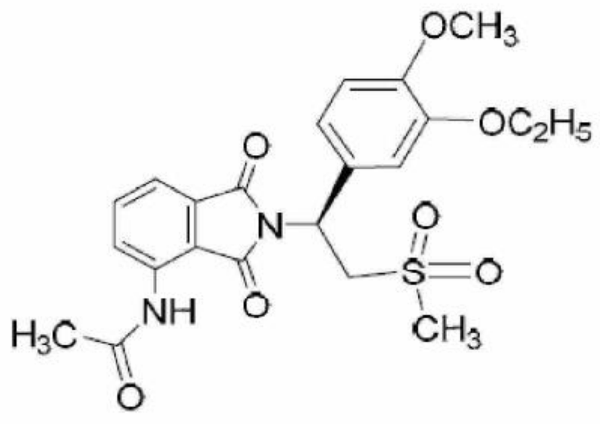
80. Zydus's ANDA Products are a solid pharmaceutical composition that are to be formulated as 10 mg, 20 mg, and 30 mg tablets intended for oral administration. *See* ZSF (A2) ¶ 4 (ECF No. 422).

81. The Zydus ANDA references Amgen's NDA No. 205437. JSF ¶ 95 (ECF No. 422).

82. Zydus's prescribing information states that Zydus's ANDA Product will be indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. *See* ZSF (A2) ¶ 5 (ECF No. 422).

83. The active pharmaceutical ingredient ("API") in Zydus's ANDA Product is apremilast, which Zydus's ANDA gives the chemical name N-[2-[(lS)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-l,3-dioxo-lH-isoindol-4-yl] acetamide. *See,* ZSF (A2) ¶ 10 (ECF No. 422).

84. In its ANDA, Zydus reported that Zydus's apremilast has the structural formula:



Apremilast

See ZSF (A2) ¶ 11 (ECF No. 422).

85. Zydus's apremilast drug substance is manufactured by Cadila as described in DMF No. 032223. *See* ZSF (A2) ¶ 12 (ECF No. 422).

IV. JURISDICTION AND VENUE

86. These consolidated actions arise under the Hatch-Waxman Act for patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 100 et seq. Joint Final Pretrial Order, Section I Jurisdiction, at 1 (ECF No. 422).

87. This Court has original jurisdiction over the subject matter of these actions under 28 U.S.C. §§ 1331 and 1338, as well as under 28 U.S.C. §§ 2201 and 2202. Joint Final Pretrial Order, Section I Jurisdiction, at 1 (ECF No. 422).

88. For purposes of these actions, subject-matter jurisdiction is not disputed by any party. Joint Final Pretrial Order, Section I Jurisdiction, at 1 (ECF No. 422).

89. This court has personal jurisdiction over the parties. For purposes of these actions, personal jurisdiction is not disputed by any party. Joint Final Pretrial Order, Section I Jurisdiction, at 1 (ECF No. 422).

90. Venue is proper in this Judicial District under 28 U.S.C. §§ 1391(b), 1391(c), and 1400(b). Joint Final Pretrial Order, Section I Jurisdiction, at 1 (ECF No. 422).

91. For purposes of these actions, no party has contested venue. Joint Final Pretrial Order, Section I Jurisdiction, at 1 (ECF No. 422).

V. TRIAL WITNESSES

A. Amgen's Experts[2]

1. Stephen Davies, Ph.D., D.Sc.

92. Dr. Davies, who testified live on June 14 and June 23, is an expert in the field of organic, medicinal, and synthetic chemistry, including stereochemistry, as well as in the synthesis and characterization of molecules and their use in pharmaceuticals, and was received by the Court as such. Trial Tr. at 85:5–13, 82:9–85:4 (Davies Direct 6.14.21); *see also* JTX-50.

[2] In support of their anticipation defense for the '638 Patent, Defendants sought to introduce evidence regarding certain statements Celgene made to the European Patent Office in connection with the prosecution of a European patent, and Amgen conditionally offered rebuttal testimony from an expert in European Patent Office law and patent prosecution, Mr. Christopher Mercer. But Defendants' evidence on this score has been excluded or stricken and Mr. Mercer's testimony and documents introduced therein have been withdrawn, *see* ECF No. 465 at 2, 4 & n.1, and therefore neither the excluded evidence nor the withdrawn testimony of Mr. Mercer will be addressed.

93. Dr. Davies holds three Ph.Ds, and is currently a Professor Emeritus at the University of Oxford, and an Extraordinary Lecturer in Chemistry at New College Oxford. Trial Tr. at 83:4–7 (Davies Direct 6.14.21). While at the University of Oxford, Dr. Davies also gained over 40 years of experience conducting research. Dr. Davies' research interests are focused on synthetic organic and medicinal chemistry, and in particular, the preparation of enantiomerically pure organic compounds, including the asymmetric and stereoselective synthesis of enantiomerically pure compounds for potential therapeutic use. *See* Trial Tr. at 82:21–83:3, 83:22–25 (Davies Direct 6.14.21); *see also* JTX-50.

94. Dr. Davies has also founded numerous companies in the pharmaceutical industry, including companies focused on the preparation of compounds for potential pharmaceutical use and preparation of chiral compounds, such as Oxford Asymmetric Ltd., OxStem Limited, MuOx, Ltd., and Summit Corporation. *See* Trial Tr. at 84:4–6, 84:13–25 (Davies Direct 6.14.21); JTX-50.

95. Dr. Davies testified regarding, among other things, the scientific principles behind basic organic chemistry and stereochemistry; issues related to validity including but not limited to the priority date to which the '638 Patent Asserted Claims are entitled, non-obviousness and lack of anticipation of the '638 Patent Asserted Claims and '536 Patent Asserted Claim, objective indicia of non-obviousness of the '638 Patent Asserted Claims and the '536 Patent Asserted Claim including skepticism of apremilast due to the common structural features shared with thalidomide. Trial Tr. at 85:14–110:23 (Davies Complete Direct 6.14.21); 1298:2–1389:22 (Davies Complete Direct 6.23.21).

2. Richard Knowles, Ph.D.

96. Dr. Knowles, who testified live on June 15 and 25, is an expert in the field of biochemistry, pharmacology, and drug discovery, including in the field of PDE4 inhibitors, and

was received by the Court as such. Trial Tr. at 198:11–16, 194:5–198:10 (Knowles Direct 6.15.21); JTX-48.

97. Dr. Knowles holds a Ph.D. in Biochemistry and has over 35 years of experience in drug development. Trial Tr. at 194:2–195:9 (Knowles Direct 6.15.21); *see also* JTX-48.

98. Previously, Dr. Knowles held positions at GlaxoSmithKline, a multinational pharmaceutical company. Trial Tr. at 196:16–197:4 (Knowles Direct 6.15.21); *see also* JTX-48 (Knowles CV). Dr. Knowles successfully led biology groups of over 50 scientists, contributing to the discovery or in-licensing, characterization and progression of multiple drug candidates, including multiple compounds that, like apremilast, are PDE4 inhibitors. Trial Tr. at 196:16–197:4 (Knowles Direct 6.15.21); *see also* JTX-48.

99. In particular, Dr. Knowles oversaw a team that investigated apremilast as part of a potential in-licensing analysis. Trial Tr. at 197:5–17, 228:15–229:5 (Knowles Direct 6.15.21); *see also* JTX-48.

100. Defendants' expert, Dr. Page, acknowledges that Dr. Knowles is a "good pharmacologist." Trial Tr. at 748:12–16 (Page Cross 6.18.21).

101. Dr. Knowles testified regarding issues related to validity including but not limited to: the state of the art of PDE4 inhibitors in the 1999-2002 time period; why a POSA would not have chosen any compound of the '358 Patent as a starting point for further development for purposes of the lead compound analysis applicable to the '638 and '536 Patents, the non-obviousness of Asserted Claim 6 of the '536 Patent; objective indicia of non-obviousness of the '638 Patent and the '536 Patent; and his personal experience evaluating PDE4 inhibitors including apremilast, which was rejected for further development by Glaxo Smith Kline. Trial Tr. at 192:19–22, 198:18–240:16 (Knowles Complete Direct 6.15.21); 264:25–270:16 (Knowles Complete Redirect 6.15.21); 1660:2–1702:5 (Knowles Complete Direct 6.25.21); 1739:1–1742:8 (Knowles Complete Redirect 6.25.21).

3. Andrew Alexis, M.D., M.P.H

102. Dr. Alexis, who testified live on June 15 and 25, is an expert in the field of dermatology including the treatment of dermatologic conditions such as psoriasis, and was received by the Court as such. Trial Tr. at 275:17–22; 273:9–274:16 (Alexis Direct 6.15.21); 1742:22–1743:1 (Alexis Direct 6.25.21); *see also* JTX-47.

103. Dr. Alexis obtained his M.P.H. as well as an M.D. from Columbia University in 1999, and completed his residency in dermatology at Weill Cornell Medical Center in 2003 and his fellowship in dermatopharmacology at NYU Medical Center in 2004. JTX-47.

104. Dr. Alexis served as Chairman of the Department of Dermatology, and Director of the Skin of Color Center at Mount Sinai Morningside and Mount Sinai West in New York City. He also served as Professor of Dermatology at Icahn School of Medicine at Mount Sinai in New York City. Trial Tr. at 274:6–25; 274:18–25 (Alexis Direct 6.15.21); *see also* JTX-47. Dr. Alexis recently accepted new positions at the Department of Dermatology of Weill Cornell Medical Center and New York Presbyterian Hospital where he continues to teach medical school students and see patients respectively. Trial Tr. at 274:6–25 (Alexis 6.15.21); JTX-47.

105. Dr. Alexis is board-certified in dermatology with over twenty years of experience researching, diagnosing, and treating patients with various skin diseases and disorders, including plaque psoriasis. He is both a practicing physician, and is involved in clinical studies for psoriasis. Trial Tr. at 273:20–274:5, 275:1–3, 275:8–16 (Alexis Direct 6.15.21); *see also* JTX-47.

106. Dr. Alexis testified regarding, among other things, issues related to validity including but not limited to the non-obviousness of claim 6 of the ’536 and claims 2, 19, and 21 of the ’541 Patents; certain objective indicia of non-obviousness with respect to the ’638 and ’536 Patents Asserted Claims, including the long-felt need in the treatment of psoriasis met by Otezla, and the clinical success of Otezla in the treatment of psoriasis. Trial Tr. at 275:25–

313:21 (Alexis Complete Direct 6.15.21); 1743:19–1799:20 (Alexis Complete Direct 6.25.21); 1864:24–1869:8 (Alexis Complete Redirect 6.25.21).

4. Christopher Vellturo, Ph.D.

107. Dr. Vellturo, who testified live on June 15, is an expert in the field of microeconomics, including in the areas of survey design and implementation, and the evaluation of commercial performance of pharmaceutical products, and was received by the Court as such. Trial Tr. at 348:21–349:5, 347:2–348:20 (Vellturo Direct 6.15.21); JTX-46 at JTX-46_2.

108. He received a Sc.B. in Applied Mathematics and Economics, magna cum laude and Phi Beta Kappa, from Brown University in 1983. He also received a Ph.D. in Economics from the Massachusetts Institute of Technology in 1989. Trial Tr. at 347:18–23 (Vellturo Direct 6.15.21); JTX-46 at JTX-46_3.

109. Dr. Vellturo is the founder and president of Quantitative Economic Solutions, LLC, a microeconomic consulting firm, and has extensive experience in the valuation of intellectual property and in the assessment of economic injury/damages sustained as a result of copyright, trademark, and patent infringement. Trial Tr. at 348:1–348:97, 348:10–14 (Vellturo Direct 6.15.21); JTX-46 (Vellturo CV). From an intellectual property standpoint, he has analyzed patent infringement damages issues, commercial success and relevant nexus, and irreparable harm. *See* JTX-46 (Vellturo CV). He has also studied the pharmaceutical industry in the context of merger reviews in the United States and abroad, in private antitrust actions, and in the context of contract disputes. *See* JTX-46.

110. Dr. Vellturo testified regarding, among other things, issues related to validity including but not limited to the commercial success of Otezla® as objective indicia of non-obviousness and its nexus to the ’638 and ’536 Patents Asserted Claims. Trial Tr. at 349:9–379:4 (Vellturo Direct 6.15.21).

5. Allan S. Myerson, Ph.D.

111. Dr. Myerson, who testified live on June 16 and 24, is an expert in the field of chemical engineering, the study of crystalline forms, pharmaceutical manufacturing, and industrial applications of crystallization in pharmaceutical formulations, and was received by the Court as such. Trial Tr. at 424:19–425:4, 420:14–424:18 (Myerson Direct 6.16.21); *see also* JTX-53.

112. He earned a B.S. in Chemical Engineering from Columbia University in 1973 and his Ph.D. in Chemical Engineering from the University of Virginia in 1977. JTX-53 at JTX-53_1.

113. Dr. Myerson is a Professor of the Practice of Chemical Engineering, Department of Chemical Engineering at Massachusetts Institute of Technology. Trial Tr. at 422:1–5, 424:10–13 (Myerson Direct 6.16.21); JTX-53 at JTX-53_1. He has more than 45 years of experience in the area of crystallization science and technology, including the study of crystalline solid forms (polymorphs, pseudopolymorphs), pharmaceutical manufacturing, and industrial applications of crystallization. Trial Tr. at 422:13–17 (Myerson Direct 6.16.21); JTX-53.

114. Dr. Myerson has published approximately 280 papers in refereed scientific journals, and edited six books, most of which pertain to crystallization and related subjects. Trial Tr. at 423:9–15, 423:22–424:1 (Myerson Direct); JTX-53 at JTX-53_3–30.

115. Dr. Myerson's research accomplishments in the area of crystallization science and technology have been recognized by several awards, including The American Institute of Chemical Engineers ("AIChE") Separation Division, Clarence G. Gerhold award in 2015; the AICHE Process Development Division, Excellence in Process Development award in 2015; and the American Chemical Society award in Separation Science and Technology in 2008. JTX-53 at JTX-53_2.

116. Dr. Myerson testified regarding Zydus's infringement of claims 1 and 15 of the '101 Patent, and issues related to validity including but not limited to the priority date and non-obviousness of claims 1 and 15 of the '101 Patent and the novelty and non-obviousness of claims 2 and 27 of the '283 Patents. Trial Tr. at 425:8–463:25 (Myerson Direct 6.16.21); *see also* Trial Tr. at 484:23–488:25 (Myerson Redirect 6.16.21); 1571:23–1612:22 (Myerson Direct 6.24.21); 1633:24–1635:8 (Myerson Redirect 6.24.21) .

6. Fabia Gozzo, Ph.D.

117. Dr. Gozzo, who testified live on June 16, is an expert in synchrotron radiation, x-ray powder diffraction and structural characterization of materials and was received by the Court as such. Trial Tr. at 496:11–16, 491:19–496:10 (Gozzo Direct 6.16.21); *see also* JTX-271 at JTX-271_1.

118. Dr. Gozzo earned an M.S. in Physics from the Università degli Studi in Italy in 1989. She earned her Ph.D. in Physics from the École Polytechnique Fédérale de Lausanne in Switzerland in 1995. Trial Tr. at 495:17–496:1 (Gozzo Direct 6.16.21); *see also* JTX-271 at JTX-271_3.

119. Dr. Gozzo is the Founder, CEO, and Managing Director of Excelsus Structural Solutions ("ESS"). Trial Tr. at 496:6–9 (Gozzo Direct 6.16.21); *see also* JTX-271 at JTX-271_1.

120. Through ESS, Dr. Gozzo provides synchrotron radiation based analytical services and scientific consulting in the field of structural characterization of materials and quantitative phase analysis. She has extensive experience and expertise in, among other things, X-ray powder diffraction, including synchrotron XRPD, and instrumentation for crystal structure phase determination, identification, and quantification. Trial Tr. at 495:22–496:10 (Gozzo Direct 6.16.21); JTX-271 at JTX-271_1.

121. Dr. Gozzo testified regarding Zydus's infringement of the '101 Patent Asserted Claims, specifically regarding synchrotron x-ray powder diffraction analysis performed on samples of Zydus's ANDA Products, excipients, and drug substance produced during this litigation. Trial Tr. at 496:18–511:9 (Gozzo Direct 6.16.21).

7. William Smith, Esq.

122. Mr. Smith, who testified live on June 24, is an expert in United States Patent and Trademark Office ("Patent Office") policies, practices, and procedures and was received by the Court as such. Trial Tr. at 1534:7–1536:21 (Smith Direct 6.24.21).

123. Mr. Smith has a Bachelor's in Chemical Engineering from the Georgia Institute of Technology and a J.D. from the University of Baltimore. Trial Tr. at 1534:13–16 (Smith Direct 6.24.21). He is currently Of Counsel at Adam R. Stephenson Ltd., where he advises clients on issues of Patent Office policy, practice, and procedure. Trial Tr. at 1536:4–14 (Smith Direct 6.24.21).

124. Mr. Smith has more than 33 years of experience working at the Patent Office, over 19 of which were as an Administrative Patent Judge, and over 13 of which were as a patent examiner. Trial Tr. at 1534:17–1535:15 (Smith Direct 6.24.21).

125. During his time in the Patent Office, Mr. Smith was an instructor at the Patent Office's Patent Academy, where he taught and trained patent examiners. Trial Tr. at 1535:16–1536:3 (Smith Direct 6.24.21).

126. Mr. Smith testified regarding issues related to Patent Office policies, practices, and procedures including but not limited to: the examination and prosecution of the '101 Patent; the patent-term adjustment awarded to the '101 Patent; the reasons for the difference in term of the '101 Patent and the '243 Patent; the examination and prosecution of the '638 Patent; the patent-term adjustment and patent-term extension awarded to the '638 Patent; the reasons for

the difference in term of the ’638 Patent and the ’283 Patent; and the patent-term adjustment / patent-term extension tradeoff. Trial Tr. at 1536:24–1568:12 (Smith Direct 6.24.21).

B. Defendants’ Experts[3]

1. Dr. Gribble, Ph.D.[4]

127. Dr. Gribble, who testified live on June 18, is a Professor of Chemistry, Emeritus, and a Research Professor of Chemistry at Dartmouth College, Hanover, New Hampshire. Trial Tr. at 569:19–570:9 (Gribble Direct 6.18.21); JTX-59 at JTX-59_3.

128. Dr. Gribble was admitted as an expert in chemistry, organic chemistry, and medicinal chemistry, including stereochemistry and their use and development of pharmaceutical compositions. Trial Tr. at 574:2–9, 569:2–574:1 (Gribble Direct 6.18.21).

129. Dr. Gribble gave testimony related to the validity of the ’638 and ’536 Patents. Trial Tr. at 574:13–618:4 (Gribble Direct 6.18.21).

130. Dr. Gribble was impeached on several occasions. Trial Tr. at 641:2–642:24, 647:11–648:11, 648:1–649:15, 658:5–17, 676:6–677:22 (Gribble Cross 6.18.21).

2. Clive Page, Ph.D.

131. Dr. Page, who testified live on June 18, is currently a Professor of Pharmacology and Head of the Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science, King’s College London (“KCL”). Trial Tr. at 690:3–8, 690:16–691:11 (Page Direct 6.18.21); JTX-57 at JTX-57_3.

132. Dr. Page was admitted as an expert in pharmacology and drug discovery, including in the field of PDE4 inhibitors and the treatment of inflammatory diseases. Trial Tr. at 695:25–17, 689:3–696:8 (Page Direct 6.18.21).

---

[3] Defendants did not offer an expert in Patent Office policy, practice, and procedure.

[4] Dr. Gribble also testified regarding certain statements Celgene made to the European Patent Office in connection with the prosecution of a European patent. Dr. Gribble's testimony on this issue has been stricken, and the documents about which he testified have been excluded. *See* Civ. No. 18-11026, ECF No. 465 Memorandum Order at 2, 4.

133. Dr. Page gave testimony related to the validity of the ’536 Patent. Trial Tr. at 696:19–744:7 (Page Direct 6.18.21).

3. Elaine S. Gilmore, M.D., Ph.D.

134. Dr. Gilmore, who testified live on June 21, is a dermatologist as well as the owner and Medical Director of Universal Dermatology, PLLC in Fairport, NY. Trial Tr. at 813:21–814:5 (Gilmore Direct 6.21.21); JTX-63 at JTX-63_1.

135. Dr. Gilmore was admitted as an expert in the field of dermatology and the treatment of psoriasis. Trial Tr. at 819:17–23, 813:21–819:16. (Gilmore Direct 6.21.21).

136. Dr. Gilmore gave testimony related to the validity of the ’536 and ’541 Patents. Trial Tr. at 820:1–901:11 (Gilmore Direct 6.21.21); *see also* Trial Tr. at 944:22–949:5 (Gilmore Redirect 6.21.21).

137. Dr. Gilmore did not testify that the Asserted Claim of the ’536 Patent was invalid for enablement or lack of written description. Trial Tr. at 820:1–901:11 (Gilmore Direct 6.21.21); *see also* Trial Tr. at 944:22–949:5 (Gilmore Redirect 6.21.21).

4. Daniel O. Scharfstein, ScD.

138. Dr. Scharfstein, who testified live on June 21, is currently a Professor of Biostatistics in the Department of Population Health Sciences at the University of Utah School of Medicine. Trial Tr. at 953:1–15 (Scharfstein Direct 6.21.21); JTX-64 at JTX-64_1 (Scharfstein CV).

139. Dr. Scharfstein was admitted as an expert in biostatistics Trial Tr. at 956:3–956:13, 952:2–956:1 (Scharfstein Direct 6.21.21).

140. Dr. Scharfstein gave testimony related to objective indicia of non-obviousness concerning the ’541 Patent. Trial Tr. at 956:15–993:24 (Scharfstein Direct 6.21.21).

141. Plaintiff did not address any objective indicia of non-obviousness with regard to the ’541 Patent.

142. Dr. Scharfstein's testimony was not relevant to any issue in the case.

5. Johnathan W. Steed, Ph.D.

143. Dr. Steed is a Professor of Chemistry at Durham University in Durham, United Kingdom and the editor-in-chief of the American Chemical Society Journal, Crystal Growth and Design. Trial Tr. 1066:2–19 (Steed Direct 6.22.21); JTX-58 at JTX-58_1.

144. Dr. Steed was admitted as an expert in chemistry and crystallography. Trial Tr. at 1068:12–18, 1065:19–1068:11 (Steed Direct 6.22.21).

145. Dr. Steed gave testimony related to the validity of the '101 Patent. Trial Tr. at 1068:21–1129:23; *see also* 1157:22–1158:18 (Steed Direct 6.22.21).

6. Mark J. Sacchetti, Ph.D.

146. Dr. Sacchetti is the Scientific Director of the Lenor Zeeh Pharmaceutical Experiment Station (the "Station") in the School of Pharmacy at the University of Wisconsin–Madison. Trial Tr. at 1163:8–24 (Sacchetti Direct 6.22.21).

147. Dr. Sacchetti was admitted as an expert in solid state chemistry, pharmaceutical science, polymorphism and polymorph screening. Trial Tr. at 1166:4–10, 1162:5–1166:3 (Sacchetti Direct 6.22.21).

148. Dr. Sacchetti gave testimony related to the validity of the '283 Patent. Trial Tr. at 1166:12–1192:2 (Sacchetti Direct 6.22.21); *see also* Trial Tr. at 1212:6–1213:20 (Sacchetti Direct 6.22.21).

7. Steven Miller, Ph.D.

149. Dr. Miller is the owner and president of H&M Analytical Services (H&M), a cGMP laboratory. Trial Tr. at 1217:15–1218:24 (Miller Direct 6.22.21).

150. Dr. Miller gave testimony related to Zydus's infringement of the '101 Patent. Trial Tr. at 1216:17–1257:24 (Miller Direct 6.22.21).

151. Dr. Miller was admitted as an expert in characterization, identification, and analysis of polymorphs. Trial Tr. at 1220:17–23, 1216:17–1220:16 (Miller Direct 6.22.21).

152. Dr. Miller is not an expert in pharmaceutical handling, pharmaceutical storage, pharmaceutical packaging, or crystallization. Trial Tr. at 1258:17–1260:8, 1262:24–1263:24 (Miller Cross 6.22.21).

153. Dr. Miller is not qualified to opine on issues related to pharmaceutical handling, pharmaceutical storage, pharmaceutical packaging, or crystallization. Trial Tr. at 1258:17–1260:8, 1262:24–1263:24 (Miller Cross 6.22.21).

8. Ivan T. Hofmann, C.P.A., C.F.F., C.L.P.

154. Mr. Hofmann, who testified live on June 21 and June 22, is a Vice President and Managing Director at Gleason IP ("Gleason"). Trial Tr. at 1006:21–1007:2 (Hofmann Direct 6.21.21); JTX-62 at JTX-62_1 (Hofmann CV).

155. Mr. Hofmann earned a Bachelor's in Accounting and Economics from the University of Notre Dame in 1994. JTX-62 at JTX-62_1 (Hofmann CV). He does not have an advanced degree. Trial Tr. at 1042:2–3 (Hofmann Cross 6.22.21). Mr. Hofmann was admitted as an expert in pharmaceutical economics. *See* Trial Tr. at 1008:20–25 (Hofmann Direct 6.21.21).

156. Mr. Hofmann gave testimony related to whether Otezla® is a commercial success. *See* Trial Tr. at 1009:2–1022:1 (Hofmann Direct 6.21.21); 1028:24–1041:4 (Hofmann Direct 6.22.21).

C. Inventors of the Patents in Suit

1. Peter Schafer, Ph.D.

157. Dr. Peter Schafer, who testified live on June 14, is one of the named inventors of the '536, '101, '283, and '638 Patents. Trial Tr. at 129:7–9 (Schafer Direct 6.14.21).

158. Dr. Schafer received his Ph.D. from Northwestern University in biochemistry, molecular biology and cell biology in 1996. Trial Tr. at 129:10–12 (Schafer Direct 6.14.21).

159. Dr. Schafer is Scientific Vice President of Translational Medicine at Bristol-Myers Squibb Co. ("BMS"). Trial Tr. at 129:2–6 (Schafer Direct 6.14.21). Dr. Schafer joined Celgene in April 1999, and was with Celgene for more than 20 years, until November 2019, when Celgene was acquired by BMS. Trial Tr. at 129:19–23, 169:10–14 (Schafer Direct 6.14.21).

160. Dr. Schafer testified about, among other things, the history of Celgene's thalidomide analog drug discovery program, the research and development leading to the discovery of apremilast, Celgene's efforts to license for the SelCID program generally, and apremilast in particular, and the rejection of such offers by at least eleven pharmaceutical companies during the period between 1999 and 2004. Trial Tr. at 128:24–169:24 (Schafer Direct 6.14.21).

2. George Muller, Ph.D.

161. Dr. Muller, who testified by deposition designation on June 16, is an inventor of the '536, '101, '283, and '638 Patents. Trial Tr. at 518:12–13 (Muller Deposition Designation 6.16.21).

162. Dr. Muller's testimony was related to the research and development of the '536, '101, '283, and '638 Patents. Trial Tr. at 518:16–524:7 (Muller Deposition Designation 6.16.21).

3. Jean Xu

163. Ms. Xu, who testified by deposition designation on June 16, is an inventor of the '101 Patent. Trial Tr. at 535:21–536:6 (Xu Deposition Designation 6.16.21).

164. Ms. Xu's testimony was related to the research and development of the '101 Patent. Trial Tr. at 535:14–542:21 (Xu Deposition Designation 6.16.21).

D. Additional Trial Witnesses

1. Patricia Rohane, M.D.

165. Dr. Rohane, who testified by deposition designation on June 16, performed clinical development work at Celgene and joined Celgene in 2003. Trial Tr. at 525:19–25 (Rohane Deposition Designation 6.16.21).

166. Dr. Rohane's testimony was related to the research and development of the Otezla titration schedule and issues relating to thalidomide. Trial Tr. at 525:14–533:25 (Rohane Deposition Designation 6.16.21).

2. Richard Person, Ph.D.

167. Dr. Person, who testified by deposition designation on June 16, was a corporate designee for Amgen under Federal Rule of Civil Procedure 30(b)(6). Trial Tr. at 543:2–4 (Person Deposition Designation 6.16.21).

168. Dr. Person's testimony was related to Amgen's acquisition of Otezla. Trial Tr. at 543:8–550:11 (Person Deposition Designation 6.16.21).

3. Susan Kim, Pharm.D.

169. Dr. Kim, who testified by deposition designation on June 24, was a corporate designee for Amgen under Federal Rule of Civil Procedure 30(b)(6). Trial Tr. at 1637:11–25 (Kim Deposition Designation 6.24.21).

170. Dr. Kim's testimony was related to commercial and marketing issues related to Otezla. Trial Tr. at 1636:24–1649:10 (Kim 6.24.21) (entire deposition designation of Dr. Kim).

VI. CLAIM CONSTRUCTION

171. On January 15, 2020, the parties agreed to constructions for the following claim terms of the asserted claims of the patents-in-suit (ECF No. 187):

Table 1 - Agreed-to Claim Constructions

Claim Term **(Patent Claim(s))**	**Agreed-to Constructions**
"stereomerically pure" '638 Patent: claims 3 and 6 '536 Patent: claim 6 '541 Patent: claims 2, 19, and 21	"a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound"
"stereomerically pure [(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione/compound]" '638 Patent: claims 3 and 6 '536 Patent: claim 6 '541 Patent: claims 2, 19, and 21	"a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound, wherein that one stereoisomer is (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione"
"enantiomerically pure" '101 Patent: claims 1 and 15	"a stereomerically pure composition of a compound having one chiral center"

VII. TECHNICAL AND HISTORICAL BACKGROUND RELATED TO THE '638 AND '536 PATENTS

A. Stereochemistry, Racemates, and Enantiomers

172. Stereochemistry is the science of the structures and properties of molecules in three dimensions. Trial Tr. at 83:16–17 (Davies Direct 6.14.21).

173. To convey a three-dimensional structure on paper, chemists use wedges and dashed wedges. Trial Tr. at 89:4–90:11 (Davies Direct 6.14.21). Wedges represent a bond that comes forward from the perspective of the observer. Trial Tr. at 89:20–22 (Davies Direct 6.14.21). Dashed wedges represent a bond that extends away from the observer. Trial Tr. at 89:24–90:3 (Davies Direct 6.14.21). In certain circumstances, distinguishing the three-dimensional structure from the two-dimensional structure of a compound will result in different

molecules in three dimensions. Trial Tr. at 90:19–21 (Davies Direct 6.14.21). In particular, two compounds can be mirror images of each other, but cannot be superimposed on one another, because the compounds are not symmetrical. Trial Tr. at 91:8–92:21 (Davies Direct 6.14.21); *see also* PDX-model.

174. Compounds that have the same connections as depicted in a two-dimensional structure but are different in three dimensions are called stereoisomers. Trial Tr. at 92:22–93:3 (Davies Direct 6.14.21). Two mirror image stereoisomers that cannot be superimposed on one another are called enantiomers. Trial Tr. at 92:24–93:2 (Davies Direct 6.14.21).

175. Enantiomers can be differentiated experimentally by exposure to polarized light, because a pair of mirror image enantiomers will rotate polarized light in different directions. Trial Tr. at 93:9–11 (Davies Direct 6.14.21).

176. A racemate is a compound that is composed of a 50:50 mixture of two enantiomers. Trial Tr. at 94:13–14 (Davies Direct 6.14.21).

177. Stereomerically pure enantiomers are different compounds, or different entities from their corresponding racemates. Trial Tr. at 90:19–22, 94:17–21 (Davies Direct 6.14.21); 1335:22–1336:2 (Davies Direct 6.23.21); Trial Tr. at 642:14–24 (Gribble Cross 6.18.21).

178. A chemist, looking at the name of a compound, would understand that if there is no symbol before the name or other information, the name refers to the racemic mixture. Trial Tr. at 95:17–20 (Davies Direct 6.14.21).

179. Chemists name a specific enantiomer in accordance with two conventions. Trial Tr. at 93:7–8 (Davies Direct 6.14.21). Under the first convention, because the only difference between the physical properties of two pure enantiomers is whether the enantiomer rotates polarized light clockwise or counterclockwise, a chemist may refer to the enantiomer that rotates polarized light clockwise the plus (+) enantiomer, and the enantiomer that rotates polarized light counterclockwise the minus (-) enantiomer. Trial Tr. at 93:16–19 (Davies Direct

6.14.21). Under the second convention a chemist may name enantiomers using an entirely different man-made convention, which allows chemists to unambiguously name an enantiomer using man-made rules with the labels "R" or "S". Trial Tr. at 93:21–23, 94:1–10 (Davies Direct 6.14.21).

180. Whether the "R" or "S" is used for the enantiomer of a particular compound does not relate to the use of "R" or "S" for a different compound. Trial Tr. at 1488:18–1489:13 (Davies Redirect 6.23.21). For a given class of compounds, use of the "R" or "S" labelling can change based on what appear to be only minor changes to the substituents of the compound. Trial Tr. at 1488:18–1489:13 (Davies Redirect 6.23.21).

181. There is no relationship between the physical measurement of polarized light resulting in the +/- naming convention, and the man-made rules chemists use to produce the R/S naming convention. Trial Tr. at 93:23–25 (Davies Direct 6.14.21).

182. Two enantiomers that are mirror images of one another will have identical physical properties apart from their rotation of polarized light; for example, this means the enantiomers will have identical melting points and solubility. Trial Tr. at 96:4–9 (Davies Direct 6.14.21).

183. In contrast to the similar physical properties between enantiomers, the racemate has different intermolecular forces, and will have a different melting point and solubility from the two enantiomers. Trial Tr. at 96:10–13 (Davies Direct 6.14.21).

184. The racemate may have the same or different biological properties as the two enantiomers, and one enantiomer may have the same or different biological properties of the other enantiomer; when it comes to biological properties, anything is possible. Trial Tr. at 96:17–24 (Davies Direct 6.14.21).

185. A molecule must be able to interact with a particular receptor in order to elicit the biological effects of that receptor. Trial Tr. at 1345:13–16 (Davies Direct); *see also* PDX-

11 at PDX-11_18 (animation of interaction between molecules and receptor). Different receptors have different numbers of parts that can trigger a biological effect. Trial Tr. at 1345:4–1346:7 (Davies Direct 6.23.21). Depending upon the number of parts of a receptor, and the orientation of these parts, one enantiomer of a racemate may be able to completely align and elicit the full biological effect from the receptor, while the opposite enantiomer may not be able to align and elicit the full biological effect. Trial Tr. at 1345:13–19 (Davies Direct 6.23.21). Depending on the receptor, it is also possible that both enantiomers may be able to elicit the full biological effect from the receptor. Trial Tr. at 1345:22–1346:7 (Davies Direct 6.23.21).

186. A chemist would not know how biological properties of racemates and the individual enantiomers, such as potency, compare without running experiments. Trial Tr. at 96:17–25 (Davies Direct 6.14.21).

187. As of 1999, little was known about the receptor binding site of PDE4. Trial Tr. at 1346:8–11 (Davies Direct 6.23.21).

B. Overview of the Drug Discovery Process

188. The discovery and development of a new drug is a complex process, which requires significant amounts of testing of, among other things, the chemical and biological properties of a compound by a team of scientists, including chemists, pharmacologists, biologists, and clinicians. Trial Tr. at 650:1–14 (Gribble Cross 6.18.21).

189. In the drug discovery process, the POSA would have started by analyzing potential biological targets and known compounds, i.e., compounds that had been used previously for the biological targets. Trial Tr. at 1308:2–10 (Davies Direct 6.14.21).

190. The standard procedure in drug discovery is to identify a lead compound and further modify it. Trial Tr. at 650:20–23 (Gribble Cross 6.18.21). Data will guide the POSA in identifying a drug candidate. Trial Tr. at 651:20–23 (Gribble Cross 6.18.21); 1308:11–14

(Davies Direct 6.23.21) ("You select compounds . . . based on data. You need some data about the compounds in order to know that such compounds are likely to give you a starting point for your drug discovery program"). A lead compound is one that compared to other compounds, has shown good activity and no toxicity. Trial Tr. at 651:7–10 (Gribble Cross 6.18.21). To assess activity and toxicity, the actual numerical values generated by biological testing matter. Trial Tr. at 651:11–14 (Gribble Cross 6.18.21); 1310:8–18 (Davies Direct 6.23.21).

191. After identifying the lead compound, the POSA would pick some aspect of the lead compound to modify. Trial Tr. at 1308:20–25 (Davies Direct 6.23.21).

192. Modifications to the lead compound would be made using a data-driven, iterative process: by making one change to the structure at a time and conducting necessary testing, the POSA would be able to tell how the modifications affect the biological properties of the compounds. Trial Tr. at 1308:20–25 (Davies Direct 6.23.21). Eventually, after many rounds of modifications to the compound, the POSA might be able to have a compound with a suitable set of properties for further studies, and hopefully can be put into the clinic. Trial Tr. at 1308:20–25 (Davies Direct 6.23.21).

193. To advance a compound to clinical trials, the POSA would need a number of different types of data from both *in vitro* and *in vivo* studies, including efficacy, toxicity, bioavailability, and stability. Trial Tr. at 651:20–652:8 (Gribble Cross 6.18.21).

194. A POSA has limited time and resources. Given these temporal and economic constraints on drug discovery, the POSA would not have had unlimited resources to synthesize every possible compound and conduct every possible test. Trial Tr. at 652:9–11 (Gribble Cross 6.18.21); 1310:1–13 (Davies Direct 6.23.21).

195. Drug development takes years of effort, with no guarantee of success. Trial Tr. at 1311:16–24 (Davies Direct 6.23.21). Only a tiny percentage of compounds that are synthesized in the lab result in a marketed drug. Trial Tr. at 652:12–15 (Gribble Cross 6.18.21);

144:19–22 (Schafer Direct 6.14.21). For every approximately 10,000 compounds synthesized in the lab, maybe one will make into Phase 2 clinical studies. Trial Tr. at 652:12–20 (Gribble Cross 6.18.21). Finding a new drug that makes it onto the market is like finding a needle in a haystack. Trial Tr. at 652:25–653:7 (Gribble Cross 6.18.21).

196. The reasons a given drug might not make it all the way to FDA approval usually comes down to three things: a safety problem, a tolerability problem, or a lack of efficacy. Trial Tr. at 144:23–145:1 (Schafer Direct 6.14.21).

C. Discovery of Apremilast

1. Celgene's SelCID Drug Discovery Program

197. In 1992, Celgene started to work on an "unusual" project: it in-licensed thalidomide from Rockefeller University. Trial Tr. at 131:2–19 (Schafer Direct 6.14.21). Celgene's strategy was to develop analogs of thalidomide that were anti-inflammatory but were better and safer than thalidomide. Trial Tr. at 130:6–131:19, 133:20–23 (Schafer Direct 6.14.21); PTX-849 at PTX-849_2.

198. Using the structure of thalidomide as the template, Celgene developed two classes of thalidomide analogs, one of which is called Selective Cytokine Inhibitory Drugs ("SelCIDs"). Trial Tr. at 135:7–14 (Schafer Direct 6.14.21); 519:1–11 (Muller Deposition Designation 6.16.21); PTX-940 at PTX-940_5. The other class is called Immunomodulatory Drugs ("IMiDs"). PTX-940 at PTX-940_5; Trial Tr. at 136:5–7 (Schafer Direct 6.14.21).

199. SelCID is a name that Celgene created and trademarked. Trial Tr. at 135:12–136:4 (Schafer Direct 6.14.21).

200. Celgene discovered that SelCIDs had the potential to inhibit both PDE4 and TNFα, while IMiDs did not inhibit PDE4 at therapeutically useful levels. Both SelCIDs and IMiDs had the potential to inhibit TNFα. Trial Tr. at 135:15–17, 136:5–7, 137:2–6 (Schafer Direct 6.14.21); 519:17–21 (Muller Deposition Designation 6.16.21); JTX-66 at JTX-66_4.

201. Not all TNFα inhibitors are PDE4 inhibitors; for example, thalidomide inhibits TNFα, but does not inhibit PDE4. JTX-69 at JTX-69_1, JTX-69_4.

202. Apremilast is a SelCID. Trial Tr. at 136:8–9 (Schafer Direct 6.14.21).

203. For Celgene's SelCID drug discovery program, it was aiming to develop small molecules that could be taken orally, e.g., in a capsule or tablet, that would have anti-inflammatory properties for the treatment of diseases such as psoriasis, arthritic conditions, and inflammatory bowel diseases. Trial Tr. at 136:10–15, 137:7–16, 138:4–6 (Schafer Direct 6.14.21).

204. Oral drugs, like pills, are generally considered more convenient and are generally preferred by patients over injected drugs. Trial Tr. at 137:17–138:3 (Schafer Direct 6.14.21); 586:22–587:2 (Gribble Direct 6.18.21); 876:11–19 (Gilmore Direct 6.21.21).

205. As part of its drug development program of SelCIDs, Celgene conducted a number of primary screens on its PDE4 compounds. Trial Tr. at 140:18–141:9 (Schafer Direct 6.14.21).

206. The primary screens Celgene ran included a PDE4 enzyme assay, TNFα cellular inhibition assays in human peripheral blood mononuclear blood cells and human whole blood cells; and a PDE4 selectivity assay. Trial Tr. at 140:18–141:9 (Schafer Direct 6.14.21).

207. In 1999, PDE4 was being intensively studied as a therapeutic target by many, if not most, pharmaceutical companies. *See* PF ¶¶ 512–19.

208. In 1999, it was not common for the companies that were working on PDE4 inhibitors to focus on inhibition of TNFα. Trial Tr. at 141:19–142:2 (Schafer Direct 6.14.21).

209. Companies working on PDE4 inhibitors did not focus on TNFα because most of those companies were interested in asthma or chronic obstructive pulmonary disease ("COPD"), and TNFα was not thought to be involved in those diseases. Trial Tr. at 141:19–142:5 (Schafer Direct 6.14.21).

210. While other companies were focused on either TNFα or PDE4 inhibitors, Celgene was looking for a compound that had similar potency in both the PDE4 enzyme assay and the TNFα cellular assay. Trial Tr. at 141:11–14 (Schafer Direct 6.14.21).

211. Selectivity for PDE4 was important to Celgene because "if you hit other PDEs, like PDE3 or PDE7 or any of the others, you may have additional side effects." Trial Tr. at 142:612 (Schafer Direct 6.14.21).

212. Celgene was looking for a compound that was potent, selective for PDE4, and had drug-like properties, like absorption, stability, activity *in vivo*, was safe in animals and was tolerable. Trial Tr. at 142:16–143:10 (Schafer Direct 6.14.21).

213. Celgene's primary screens took approximately one month to complete per compound. Trial Tr. at 143:11–15 (Schafer Direct 6.14.21).

214. As of early 1999, when Dr. Schafer joined Celgene, Celgene was a small pharmaceutical company, with approximately 125 employees. Trial Tr. at 129:22–130:5 (Schafer Direct 6.14.21).

2. CDC-801

215. In 1994, Celgene synthesized CDC-801. Trial Tr. at 138:10–14 (Schafer Direct 6.14.21).

216. CDC-801 was the code name Celgene used externally. Within Celgene, the compound was called CC-1088. Trial Tr. at 138:15–22 (Schafer Direct 6.14.21).

217. CDC-801 is a racemate. Trial Tr. at 138:23–24 (Schafer Direct 6.14.21).

218. Celgene found that CDC-801 had a PDE4 IC_{50} of 15 µM and a TNFα IC_{50} in human peripheral blood mononuclear blood cells of 21 µM. Trial Tr. at 138:10–14 (Schafer Direct 6.14.21); PTX-940 at PTX-940_67.

219. In 1997, Celgene advanced CDC-801 into Phase I clinical trials. Trial Tr. at 138:25–139:1 (Schafer Direct 6.14.21). It was the first SelCID that Celgene advanced into the clinic. PTX-849 at PTX-849_5.

220. As part of the SelCID drug discovery program, Celgene continued synthesizing new SelCIDs even after CDC-801 entered into Phase I clinical trials. Trial Tr. at 139:2–4 (Schafer Direct 6.14.21).

221. CDC-801 was never FDA approved, and was abandoned by Celgene because it did not show adequate activity. Trial Tr. at 139:5–10 (Schafer Direct 6.14.21).

3. CC-7085

222. The second SelCID Celgene advanced into Phase I clinical trials was CC-7085. Trial Tr. at 139:11–16 (Schafer Direct 6.14.21).

223. CC-7085 was synthesized in 1998, and like CDC-801, was a racemate. Trial Tr. at 139:15–18 (Schafer Direct 6.14.21); PTX-849 at PTX-849_5.

224. Dr. Hon-Wah Man, a member of the Celgene chemistry department, synthesized CC-7085 along with other "phenethylsulfone" thalidomide analogs in 1997-1998, all of them racemates. *See* PTX-850 at PTX-850_17, PTX-851 at PTX-851_13, PTX-853 at PTX-853_15, JTX-184 at JTX-184_9.

225. CC-7085 was in pre-clinical development as of April 1999, and was put into clinical trials in late 2000. Trial Tr. at 140:10–12, 139:19–21 (Schafer Direct 6.14.21).

226. Although not publicly known, CC-7085 is the same compound as Example 12 in the '358 Patent. Trial Tr. at 1370:19–23 (Davies Direct 6.23.21); 139:25–140:9 (Schafer Direct 6.14.21).

227. CC-7085 was the code number used internally at Celgene. CC-7085 was also given the code name CDC-998 for external communications. Trial Tr. at 139:22–140:2 (Schafer Direct 6.14.21). The structure of CDC-998 was not known publicly. JTX-282 at JTX-

282_2 (in Table 1, footnote c, observing for CDC-998 that the "structure not yet disclosed"); *see also generally* JTX-66 (noting that the structure for CDC-998 was not publicly known); Trial Tr. at 1699:6–10 (Knowles Direct 6.25.21).

228. Celgene used an alternative set of code names for its compounds, the CDC names, to protect the identity of the structures of these compounds from being known externally. Trial Tr. at 140:3–9 (Schafer Direct 6.14.21).

229. Between early 1998, when Celgene synthesized CC-7085, and late 1999, Celgene continued to make many new SelCIDs. Trial Tr. at 144:4–8 (Schafer Direct 6.14.21); JTX-156; JTX-179; JTX-106; PTX-853. In particular, Celgene synthesized a number of CC-7085 analogs. JTX-156 at JTX-156_6.

230. Celgene continued to make additional compounds because it "was trying to optimize potency, selectivity, trying to minimize safety and tolerability problems, and you just never know with the compound that you have if they're going to be good enough." Trial Tr. at 144:9–18 (Schafer Direct 6.14.21).

231. Over the years, as part of the thalidomide analog drug discovery program, Celgene made and tested hundreds, if not thousands, of compounds. Trial Tr. at 172:15–18 (Schafer Direct 6.14.21); *see also* JTX-156, JTX-179; JTX-210; JTX-106; PTX-850; PTX-851; PTX-852; PTX-853.

4. Apremilast (CC-10004)

232. Dr. Hon-Wah Man first synthesized apremilast on October 21, 1999. JTX-210 at JTX-210_44; JTX-148 at JTX-148_1; Trial Tr. at 144:2–3 (Schafer Direct 6.14.21); 1303:16–1304:5 (Davies Direct 6.23.21).

233. As of October 1999, Dr. Muller was the head of the chemistry department at Celgene. Trial Tr. at 172:1–3 (Schafer Cross 6.14.21).

234. Apremilast is an S-enantiomer with a structure that is related to the structure of CC-7085, which is a racemic mixture. Trial Tr. at 143:22–144:1 (Schafer Direct 6.14.21); 520:23–521:3 (Muller Deposition Designation 6.16.21) ("CC-7085 is a racemic [compound] … which would be an equimolar ratio of the R and S-enantiomers with the S-enantiomer being what is now known as apremilast").

235. Apremilast had the internal name CC-10004. In external presentations, apremilast was referred to as CC-110004. Trial Tr. at 145:2–6 (Schafer Direct 6.14.21).

236. Celgene also synthesized the opposite enantiomer of apremilast, which was known internally at Celgene as CC-10007. Trial Tr. at 145:7–9 (Schafer Direct 6.14.21).

237. Dr. Schafer was involved in the testing of apremilast and also involved in the discussion with outside collaborators, like GSK regarding apremilast. Trial Tr. at 145:10–19 (Schafer Direct 6.14.21).

238. As part of the SelCID drug discovery program, Celgene chemists and biologists summarized the work they did, namely "the new compounds that were made and tested" each month in monthly reports. Trial Tr. at 145:25–146:5 (Schafer Direct 6.14.21).

a) Early preclinical testing of apremilast

239. The November 1999 monthly report indicated that apremilast had a lower IC_{50} in both the TNFα and PDE4 assays than CC-7085 and CC-10007. Trial Tr. at 146:20–147:8 (Schafer Direct 6.14.21); JTX-106 at JTX-106_2.

240. Apremilast was first tested *in vivo* in the murine shock model, and the result was reported in the December 1999 monthly report. Trial Tr. at 147:21–24, 148:9–14 (Schafer Direct 6.14.21); JTX-156 at JTX-156_1. The murine shock model is the mouse model where a bacterial endotoxin was used to elicit an inflammatory response. Trial Tr. at 147:12–16 (Schafer Direct 6.14.21).

241. The murine shock model is part of the "necessary regimen of testing," and is a complicated mouse model that provides data as to whether a compound is absorbed from an oral dose, reaches the site of action in the body through the blood, and whether the compound lasts long enough in the body for it to have its intended effect. Trial Tr. at 239:8–19 (Knowles Direct 6.15.21); 173:18–25 (Schafer Cross 6.14.21).

242. If a compound did not work in the murine shock model, Celgene would not test it further. Trial Tr. at 174:1–7 (Schafer Cross 6.14.21).

243. In the murine shock model, compounds were administered to the mouse orally using a gavage needle. Trial Tr. at 147:25–148:8 (Schafer Direct 6.14.21); JTX-179 at JTX-179_14. A gavage needle is a thin metal tube that administers the compound, mixed with a liquid such as water, down the esophagus of the mouse. Trial Tr. at 148:4–8 (Schafer Direct 6.14.21).

244. Apremilast was administered to the mouse in a dose of 1 mg/kg po, and had an ED_{50} value of 0.05 mg/kg. Trial Tr. at 148:21–149:4, 154:22–25 (Schafer Direct 6.14.21); JTX-156 at JTX-156_1; JTX-179 at JTX-179_13–14; JTX-114 at JTX-114_18. A lower ED_{50} suggests higher potency. Trial Tr. at 154:19–21 (Schafer Direct 6.14.21). "po" means "per os" and is a Latin abbreviation for "by mouth." Trial Tr. at 149:2–4 (Schafer Direct 6.4.21).

245. Apremilast's TNFα ED_{50} of 0.05 mg/kg in the mouse model was a 20-fold increase in potency compared to the racemate, CC-7085. Trial Tr. at 154:22–25 (Schafer Direct 6.14.21).

246. The 20-fold increase was a surprising result. One would typically expect at most a two-fold difference in potency as between a racemate and an enantiomer. Trial Tr. at 155:1–15 (Schafer Direct 6.14.21).

247. The fact that apremilast had excellent potency in the murine model demonstrated that all of the steps required in the mouse's complicated system to move the

compound from administration to the site of action have been met. Trial Tr. at 239:8–19 (Knowles Direct 6.15.21). If an average 70 kg human had been administered the same 1 mg/kg po dose, that human would have received 70 mg of apremilast. Trial Tr. at 149:5–9 (Schafer Direct 6.14.21).

248. Celgene tested apremilast in a number of other assays, including for selectivity against other PDEs and for efficacy/emesis in ferrets. JTX-3 at 22:30–29:40.

b) PDE4A4 ratio of apremilast

249. Celgene also examined apremilast for its PDE4A4 ratio, which Celgene believed could predict the side effects of nausea and emesis. Trial Tr. at 150:23–151:3 (Schafer Direct 6.14.21).

250. Celgene determined that apremilast had a very low PDE4A4 ratio of 0.15. Trial Tr. at 151:10–20 (Schafer Direct 6.14.21); JTX-208 at JTX-208_14. Apremilast's PDE4A4 ratio of 0.15 was a good result, which predicted better tolerability in humans. Trial Tr. at 237:6–19 (Knowles Direct 6.15.21).

251. Ariflo had a PDE4A4 ratio of 1.84 and rolipram had a PDE4A4 ratio of 3.64. JTX-208 at JTX-208_14. Apremilast's PDE4A4 ratio was 10-fold better than Ariflo and 20-fold better than rolipram. Trial Tr. at 152:10–20 (Schafer Direct 6.14.21).

252. CC-7085 had a PDE4A4 ratio of 1.67. JTX-208 at JTX-208_37 (showing CC-7085 with a PDE4A4 IC_{50} of 0.09 and a PDE4A4 high IC_{50} of 0.054). Apremilast's PDE4A4 ratio was 10-fold better than CC-7085. Trial Tr. at 153:1–17 (Schafer Direct 6.14.21).

253. Celgene was excited to find that apremilast had such a low PDE4A4 ratio. Trial Tr. at 153:11–17 (Schafer Direct 6.14.21) ("Q. What was your reaction to receiving the data we just reviewed concerning the PDE4A4 ratio of apremilast compared to these other compounds? A. We were very excited. We were happy that we were getting such a low number

with this compound. You can see that that number is just about the best on the slide. And so this was . . . very exciting for us.”).

c) The ferret lung neutrophilia and emesis model

254. In 2001, GlaxoSmithKline (“GSK”), pursuant to a collaboration agreement with Celgene, evaluated apremilast and a few other compounds in a ferret lung neutrophilia and emesis model. Trial Tr. at 156:22–157:10 (Schafer Direct 6.14.21); 158:25–159:13 (Schafer Direct 6.14.21); PTX-374; JTX-118.

255. A ferret lung neutrophilia and emesis model is a useful study in which one can measure both the anti-inflammatory effect and the side effect (i.e., emesis) in the same animal. Trial Tr. at 157:11–23 (Schafer Direct 6.14.21); 229:12–25 (Knowles Direct 6.15.21); 235:20–236:7 (Knowles Direct 6.15.21); 727:20–729:25 (Page Direct 6.18.21). Ferrets are used to test emesis because ferrets, unlike rats and mice, have the capacity to vomit or retch. Trial Tr. at 157:11–23 (Schafer Direct 6.14.21); 230:1–8 (Knowles Direct 6.15.21).

256. The therapeutic index in emesis “gives some early indication of potential toxicity.” Trial Tr. at 736:17–23 (Page Direct 6.18.21); JTX-232.

257. When apremilast was tested in the ferret lung neutrophilia and emesis model, it showed efficacy at 0.8 mg/kg, and induced emetic behavior at 10 mg/kg, providing a therapeutic index of 12. Trial Tr. at 158:2–19 (Schafer Direct 6.14.21); 727:20–729:25 (Page Direct 6.18.21) (calculating therapeutic index as 12.5); PTX-374 at PTX-374_15; JTX-118.

258. Ariflo was not as potent in the ferret lung neutrophilia model, with an ED_{50} of 8, which is ten times less potent than apremilast. Trial. Tr. at 158:12–19 (Schafer Direct 6.14.21). Ariflo also induced emesis at a dose of 3 mg/kg, which is lower than the dose at which apremilast induced emesis. Trial Tr. at 158:12–19 (Schafer Direct 6.14.21). The therapeutic index for Ariflo was 0.38, thirty times less than the therapeutic index for apremilast. Trial Tr. at 158:12–19 (Schafer Direct 6.14.21).

259. Celgene was "thrilled" that apremilast was shown to have a 30-fold improvement in therapeutic index as compared to Ariflo. Trial Tr. at 159:21–160:3 (Schafer Direct 6.14.21). The data from the ferret study were important to Celgene because the data could be used to estimate the efficacious dose that would be safe for use in humans, for example, in Phase I clinical trials. Trial Tr. at 159:14–20 (Schafer Direct 6.14.21).

260. Celgene advanced apremilast into clinical studies in 2003. Trial Tr. at 160:24–161:1 (Schafer Direct 6.14.21).

261. Celgene submitted an Investigational New Drug Application to FDA to use apremilast in a Phase 2 clinical trial for psoriasis in 2004. PTX-1267 at *e.g.*, PTX-1267_1; PTX-833 at PTX-833_2; JTX-210 at JTX-210_44.

262. Otezla was approved by FDA in 2014 for the treatment of psoriatic arthritis. Trial Tr. at 168:11–14 (Schafer Direct 6.14.21). Otezla subsequently received approval for the treatment of psoriasis and Behcet's disease. Trial Tr. at 168:15–18 (Schafer Direct 6.14.21).

263. Apremilast is unique in terms of its mechanism of action. It is a small molecule that gets into the cells in the body. It exerts its anti-inflammatory effect and rebalances the immune system by blocking the production of TNFα and other cytokines. Trial Tr. at 168:19–169:2 (Schafer Direct 6.14.21).

264. To date, apremilast is the only PDE4 inhibitor approved to treat psoriasis. Unlike other drugs that are approved for psoriasis, apremilast is not immunosuppressive. Trial Tr. at 169:3–9 (Schafer Direct 6.14.21); Trial Tr. at 304:9–305:2 (Alexis Direct 6.15.21).

VIII. THE '638 COMPOSITION PATENT ASSERTED CLAIMS ARE INFRINGED

265. Both Sandoz and Zydus have stipulated to infringement of the '638 Patent. *See* SSF (A3) ¶ 9–10 (ECF No. 422); Civ. No. 18-11026, ECF No. 246; ZSF (A2) ¶ 14–15 (ECF No. 422); Civ. No. 18-11267, ECF No. 54.

A. Sandoz's Proposed ANDA Product Infringes the '638 Composition Patent

266. The submission of Sandoz's ANDA to the FDA seeking approval for Sandoz's ANDA is an act of infringement with respect to claims 3 and 6 of the '638 Patent under 35 U.S.C. § 271(e)(2)(A), if those claims are not found to be invalid or unenforceable. *See* SSF (A3) ¶ 9 (ECF No. 422); Civ. No. 18-11026, ECF No. 246.

267. Upon final approval of Sandoz's ANDA, the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Sandoz's ANDA Products will infringe claims 3 and 6 of the '638 Patent under 35 U.S.C. § 271(a), (b) and/or (c), if those claims are not found to be invalid or unenforceable. *See* SSF (A3) ¶ 10 (ECF No. 422); Civ. No. 18-11026, ECF No. 246.

B. Zydus's Proposed ANDA Product Infringes the '638 Composition Patent

268. The submission of Zydus's ANDA to the FDA seeking approval for Zydus's ANDA Products is an act of infringement with respect to claims 3 and 6 of the '638 Patent under 35 U.S.C. § 271(e)(2)(A), if those claims are not found to be invalid or unenforceable. *See* ZSF (A2) ¶ 14 (ECF No. 422); Civ. No. 18-11267, ECF No. 54.

269. Upon final approval of Zydus's ANDA, the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Zydus's ANDA Products will infringe claims 3 and 6 of the '638 Patent under 35 U.S.C. § 271(a), (b) and/or (c), if those claims are not found to be invalid or unenforceable. *See* ZSF (A2) ¶ 15 (ECF No. 422); Civ. No. 18-11267, ECF No. 54.

IX. THE '638 COMPOSITION PATENT ASSERTED CLAIMS ARE NOT INVALID

A. Person of Ordinary Skill in the Art for the '638 Patent

270. The person of ordinary skill in the art ("POSA") for the '638 Patent would have at least a Bachelor's degree in a field such as pharmaceutical chemistry, chemistry, pharmaceutics or a related discipline with about three to five years of work experience in this

area, or a comparable level of education and training, such as a Ph.D. with one to two years' experience in this area. The POSA would work as a member of a team having access to other team members with experience in designing, evaluating, and administering pharmaceutical formulations obtained by some combination of education with work experience, such as a physician with knowledge and experience relevant to any methods of treatment to which the patents are directed, if applicable. Trial Tr. at 1300:23–1301:11 (Davies Direct 6.23.21); 200:9–22 (Knowles Direct 6.15.21).

271. Regardless of the definition of a POSA used, Dr. Davies' opinions do not change. Trial Tr. at 1301:16–18 (Davies Direct 6.23.21).

272. Regardless of the definition of a POSA used, Dr. Knowles' opinions do not change. Trial Tr. at 1663:10–16 (Knowles Direct 6.25.21).

B. Claims 3 and 6 of the '638 Composition Patent Are Entitled to a Priority Date of October 21, 1999.

273. Claim 3 of the '638 Patent is entitled to a priority date of October 21, 1999. *See* PF ¶¶ 275–301.

274. Claim 6 of the '638 Patent is entitled to a priority date of October 21, 1999. *See* PF ¶¶ 275–301.

275. Claim 3 of the '638 Patent requires 1) a pharmaceutical composition; 2) that is suitable for oral administration to a patient (defined as a mammal particularly a human, JTX-3 at 5:22–23); comprising 3) stereomerically pure [apremilast] or a pharmaceutically acceptable salt, solvate or hydrate thereof; and 4) a pharmaceutically acceptable carrier, diluent or excipient. JTX-3 at cl. 3.

276. Claim 6 of the '638 Patent requires 1) a pharmaceutical composition; 2) that is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient (defined as a mammal particularly a human, JTX-3 at 5:22–23); comprising 3) 10–200 mg of 4) stereomerically pure [apremilast] or a pharmaceutically acceptable salt, solvate

or hydrate thereof; and 5) a pharmaceutically acceptable carrier, diluent or excipient. JTX-3 at cl. 6.

277. Claim 3 was conceived on October 21, 1999 and reduced to practice by no later than December 1999. Trial Tr. at 1303:5–1307:17 (Davies Direct 6.23.21); 136:8–149:9 (Schafer Direct); JTX-148; JTX-106; JTX-156; JTX-179.

278. Claim 6 was conceived on October 21, 1999 and reduced to practice by no later than December 1999. Trial Tr. at 1303:5–1307:17 (Davies Direct); 136:8–149:9 (Schafer Direct 6.14.21); JTX-148; JTX-106; JTX-156; JTX-179.

279. The inventors had conceived of an oral pharmaceutical composition of stereomerically pure apremilast and a pharmaceutically acceptable carrier, diluent or excipient as of October 21, 1999. Trial Tr. at 1303:5–15, 1306:1–10 (Davies Direct 6.23.21).

280. Dr. Hon-Wah Man synthesized apremilast on October 21, 1999. JTX-210 at JTX-210_44; JTX-148 at JTX-148_1; Trial Tr. at 144:2–3 (Schafer Direct 6.14.21); 1303:18–1304:5 (Davies Direct 6.23.21).

281. The apremilast synthesized by Dr. Man on October 21, 1999 was stereomerically pure. Trial Tr. at 1305:5–11 (Davies Direct 6.23.21); JTX-148 at JTX-148_1.

282. Dr. Man synthesized 640 mg of apremilast on October 21, 1999, 110 mg were used for PDE4 and TNFα testing, leaving 520 mg for additional testing. JTX-148 at JTX-148_1.

283. Apremilast is a SelCID. Trial Tr. at 136:8–9 (Schafer Direct 6.14.21).

284. For Celgene's SelCID drug discovery program, it was aiming to develop small molecules that could be taken orally, e.g., in a capsule or tablet, that would have anti-inflammatory properties for the treatment of diseases such as psoriasis, arthritic conditions, and inflammatory bowel diseases. Trial Tr. at 136:10–15, 137:7–16, 138:4–6 (Schafer Direct 6.14.21).

285. By October 1999, the inventors of the ’638 Patent had many years of experience with SelCIDs. Trial Tr. at 138:10–22 (Schafer Direct 6.14.21).

286. By October 1999, Drs. Man and Muller had been synthesizing and testing SelCIDs since at least 1994, when CDC-801 (also known as CC-1088) was synthesized. *See* Trial Tr. at 138:10–22 (Schafer Direct 6.14.21); PTX-849 at PTX-849_2.

287. By October 1999, Dr. Schafer began testing SelCIDs after he joined Celgene in April 1999. Trial Tr. at 129:22–23, 132:15–19, 145:10–19 (Schafer Direct 6.14.21); *see also* PF ¶¶ 205–13.

288. Celgene scientists had even taken a SelCID, CDC-801 into Phase I clinical studies in 1997. Trial Tr. at 138:25–139:1 (Schafer Direct 6.14.21).

289. CC-7085 was in pre-clinical development as of April 1999, and was put into clinical trials in late 2000. Trial Tr. at 140:10–12, 139:19–21 (Schafer Direct 6.14.21).

290. If a compound has been taken into clinical studies in the U.S., that means that a company has submitted an Investigational New Drug Application to FDA that summarizes the preclinical safety and the pharmacology of the compound. Trial Tr. at 163:13–16 (Schafer Direct 6.14.21); 202:16–23 (Knowles Direct 6.15.21). As of December 1999, CC-7085 was close to beginning clinical trials; therefore, the Celgene inventors had non-public information that would further support a belief that oral pharmaceutical compositions of apremilast would work for its intended purpose. *See, e.g.*, Trial Tr. at 140:10–12, 139:19–21 (Schafer Direct 6.14.21) (noting that CC-7085 was put into clinical trials in late 2000).

291. In Celgene’s SelCID drug discovery program, the goal was to synthesize compounds to be administered eventually to humans. Trial Tr. at 1306:1–10 (Davies Direct 6.23.21); 136:10–15, 137:13–16 (Schafer Direct 6.14.21).

292. A pharmaceutical composition of stereomerically pure apremilast and a pharmaceutically acceptable carrier, diluent or excipient (e.g., water) suitable for oral

administration to a patient was reduced to practice by December 1999. Trial Tr. at 1306:11–1307:11 (Davies Direct 6.23.21).

293. The November 1999 monthly report indicated that apremilast had a lower IC_{50} in both the TNFα and PDE4 assays than CC-7085 and CC-10007. Trial Tr. at 146:20–147:8 (Schafer Direct 6.14.21); JTX-106 at JTX-106_2.

294. Apremilast was first tested *in vivo* in the murine shock model, which was reported in the December 1999 monthly report. Trial Tr. at 147:21–24, 148:9–14 (Schafer Direct 6.14.21); 1306:18–21 (Davies Direct 6.23.21); JTX-156 at JTX-156_1.

295. The murine shock model "is the mouse model where a bacterial endotoxin is used to elicit an inflammatory response." Trial Tr. at 147:12–16 (Schafer Direct 6.14.21).

296. The murine shock model is part of the "necessary regimen of testing to determine if a compound can be absorbed through the gut, if its stable, if it reaches the target tissue in the cells and if it has the desired effect." Trial Tr. at 173:18–25 (Schafer Cross 6.14.21).

297. If a compound did not work in the murine shock model, Celgene would not test it further. Trial Tr. at 174:1–7 (Schafer Cross 6.14.21).

298. The murine shock model can be used to predict a dose range which would be effective in human studies. Trial Tr. at 239:8–19 (Knowles Direct 6.15.21).

299. In the murine shock model, compounds are administered to the mouse orally using a gavage needle. Trial Tr. at 147:25–148:8 (Schafer Direct 6.14.21).

300. A gavage needle is a thin metal tube that administers the compound, mixed with a liquid such as water, down the esophagus of the mouse. Trial Tr. at 148:4–8 (Schafer Direct 6.14.21).

301. Apremilast was administered to the mouse with water in a dose of 1 mg/kg po. Trial Tr. at 148:21–149:4 (Schafer Direct 6.14.21); JTX-156 at JTX-156_1; JTX-179 at JTX-

179_13–14. "po" is a Latin abbreviation for "by mouth." Trial Tr. at 149:2–4 (Schafer Direct 6.14.21). If an average 70 kg human had been administered the same 1 mg/kg po dose, that human would have received 70 mg of apremilast. Trial Tr. at 149:5–9 (Schafer Direct 6.14.21); 1307:12–17 (Davies Direct 6.23.21).

C. Defendants Have Failed to Prove by Clear and Convincing Evidence that the '638 Composition Patent Asserted Claims Are Invalid for Anticipation.

1. U.S. Patent No. 6,020,358

302. The named inventors of the '358 Patent are Drs. George W. Muller and Hon-Wah Man. DTX-174 at DTX-174_1.

303. The '358 Patent was filed on October 30, 1998, and issued on February 1, 2000. DTX-174 at DTX-174_1.

304. The assignee of the '358 Patent is Celgene Corporation. DTX-174 at DTX-174_1.

305. Dr. Gribble did not identify the '358 Patent on his own. It was provided to him by counsel. Trial Tr. at 618:21–619:8 (Gribble Cross 6.18.21).

306. The Patent Office considered the '358 Patent during the prosecution of the '638 Patent and found that the '638 Patent is neither anticipated nor rendered obvious by the '358 Patent. JTX-16 at JTX-16_271–273; Trial Tr. at 679:1–13 (Gribble Cross 6.18.21).

307. The patent examiner reviewing the application for the '638 Patent, who is a Primary Patent Examiner and also has a Ph.D., concluded that the composition comprising stereomerically pure apremilast has not been found in the '358 Patent. JTX-16 at JTX-16_271–273; Trial Tr. at 679:10–22 (Gribble Cross 6.18.21).

a) The ’358 Patent contains Formula I, which covers billions of compounds, and seventeen example racemates.

308. The ’358 Patent claims a genus of phenethylsulfone compounds that have a thalimido group, which is a ring structure that is also present in thalidomide. Trial Tr. at 1314:5–10 (Davies Direct 6.23.21).[5]

309. Formula I of the ’358 Patent, DTX-174 at 4:66–6:18, covers a broad genus of billions of compounds. Trial Tr. at 619:13–19 (Gribble Cross 6.18.21); 1313:11–15 (Davies Direct 6.23.21).

310. The ’358 Patent identifies seventeen example compounds (Examples 3–17, 19–20) that fall within the scope of Formula I, all of which are racemates. DTX-174 at 11:5–16:39, 16:62–17:42; Trial Tr. at 619:9–1, 662:25–663:5 (Gribble Cross 6.18.21); 1315:1–17 (Davies Direct 6.23.21).

311. The ’358 Patent does not disclose any specific methods for making enantiomers of any of the seventeen example compounds, or of any of the compounds of Formula I. PF ¶¶ 381–82, 450.

312. The seventeen example compounds included in the ’358 Patent serve only “to typify the nature of [the] invention,” they are not in any way described as preferred examples. Trial Tr. at 1314:14–23 (Davies Direct 6.23.21); 1688:5–8 (Knowles Direct 6.25.21). DTX-174 at 9:64–67.

313. The POSA would not have known which example compounds of the ’358 Patent are active or inactive by just looking at their chemical structures; the POSA would have had to

[5] The thalimido group in thalidomide and the compounds of Formula I in the ’358 Patent is also referred to as a phthalimide group. *See*, *e.g.*, Trial Tr. at 658:2–3 (Gribble Cross 6.18.21) (referring to “the phthalimide ring [that] is shared by both groups of compounds”); 1314:5–10 (Davies Direct 6.23.21) (referring to the same group as a “thalimido group” which “is also present in thalidomide”).

synthesize the 17 example compounds and test them. Trial Tr. at 664:25–665:5 (Gribble Cross 6.18.21).

314. The POSA would not have been able to determine the biological properties (e.g., toxicity, pharmacokinetics, therapeutic window) of the example compounds of the ’358 Patent by just looking at their chemical structures. Trial Tr. at 665:13–21 (Gribble Cross 6.18.21); 1333:14–20 (Davies Direct 6.23.21).

b) The ’358 Patent discloses no biological data for any compound.

315. The ’358 Patent does not include biological data for any of its compounds. Trial Tr. at 626:22–627:2 (Gribble Cross 6.18.21); 1317:2–4 (Davies Direct 6.23.21); 1683:10–23 (Knowles Direct 6.25.21).

316. By March 2002, the POSA would have had no information about the biological properties of the compounds of the ’358 Patent from any other source. Trial Tr. at 1317:5–8 (Davies Direct 6.23.21).

317. The ’358 Patent provides no PDE4 or TNFα potency data for any of its compounds. Trial Tr. at 627:4–7, 627:11–14 (Gribble Cross 6.18.21); 1683:10–23 (Knowles Direct 6.25.21).

318. The ’358 Patent broadly states that “[d]ecreasing TNFα levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases.” DTX-174 at 4:35–38. The ’358 Patent also includes a statement about the utility of its compounds to inhibit *any* PDE *generally*, stating that “[t]he compounds of the present invention are useful in the inhibition of phosphodiesterases, particularly PDE III and PDE IV, and in the treatment of diseases states mediated thereby.” DTX-174 at 4:28–32.

319. There are 11 different PDEs, PDE1 through PDE11. Trial Tr. at 700:11–14 (Page Direct 6.18.21). The ’358 Patent contains no data that would have told the POSA whether

any of its compounds are selective against a particular PDE. Trial Tr. at 657:4–7 (Gribble Cross 6.18.21).

320. The POSA would not have understood that each and every compound in the ’358 Patent is a selective PDE4 inhibitor; the POSA could not have reliably concluded that the example compounds were actually active or selective against PDE4. Trial Tr. at 1686:1–13 (Knowles Direct 6.25.21); 1317:2–1318:8 (Davies Direct 6.23.21).

321. Dr. Gribble admitted that it is possible that the compounds of Formula I of the ’358 Patent, including the 17 example compounds, are selective PDE2 inhibitors, or dual inhibitors of PDE3 and PDE4. Trial Tr. at 656:22–657:3 (Gribble Cross 6.18.21); 1686:14–18 (Knowles Direct 6.25.21).

322. Claim 18 of the ’358 Patent claims “[a] method of inhibiting PDE IV in a mammal which comprises administering thereto an effective amount of a compound according to claim 1.” DTX-174 at cl. 18. Reading the ’358 Patent as a whole, the POSA would have concluded that claim 18 of the ’358 Patent claims a method of using *those* compounds of Formula I that are PDE4 inhibitors, not any of the compounds of Formula I. Trial Tr. at 1318:9–16 (Davies Direct 6.23.21); 1741:12–1742:5 (Knowles Redirect 6.25.21) (“Q. … Would the POSA have concluded that you could practice the method of inhibiting PDE4 in claim 18 using any compound in Formula I, or that you must use one that is itself a PDE4 inhibitor? A. The latter. You’d have to use one that was a PDE4 inhibitor.”).

323. Reading the ’358 Patent as a whole, it is highly unlikely that every one of the billions of the compounds of Formula I of the ’358 Patent actually reduces PDE4 or TNFα. Trial Tr. at 654:19–655:1 (Gribble Cross 6.18.21); 1686:19–1687:6 (Knowles Direct 6.25.21); 1736:6–1737:6 (Knowles Cross 6.25.21) (“Q. … The compounds of Formula I, this is what they’re saying, the inventors, are used under the supervision of qualified professional to inhibit the undesirable effects of TNFα and PDE4. That’s what it says, right? … A. So you’re going

to interpret it as billions of compounds are all decreasing TNF. That's mad."), 1735:17–22 ("Q. … And it says that the compound is, not may be used, some of the compounds could be used. It says the compounds of Formula I are used, correct? A. Are you – are you seriously suggesting that all of the billions of compounds do it, because that doesn't seem at all sensible to me").

324. The '358 Patent discloses a long list of different disease states—only one of which is psoriasis—that may potentially be treated by decreasing TNFα levels, increasing cAMP levels, and inhibiting PDE4. DTX-174 at 4:35–54.

325. A compound may inhibit PDE4 at high concentrations, but not be potent enough to be suitable for use in humans. Trial Tr. at 1687:7–17 (Knowles Direct 6.25.21).

326. The '358 Patent would not have told the POSA whether any particular compounds of the '358 Patent are sufficiently potent to be used in a pharmaceutical composition for humans, or useful in treating inflammatory diseases like psoriasis. Trial Tr. at 1687:7–17 (Knowles Direct 6.25.21).

c) Example 12 of the '358 Patent is not highlighted as a compound of interest.

327. Example 12 of the '358 Patent is a racemate. Trial Tr. at 624:12–13 (Gribble Cross 6.18.21); 1315:8–1316:3 (Davies Direct 6.23.21).

328. The '358 Patent includes nothing that would have highlighted Example 12 as opposed to the other 16 examples, or any compound within the scope of the '358 Patent. Trial Tr. at 1316:4–6 (Davies Direct 6.23.21); 1688:1–8 (Knowles Direct 6.25.21).

329. Two example compounds (Example 9 and Example 19) are highlighted in the Abstract of the '358 Patent, while Example 12 is not. DTX-174 at DTX-174_1; Trial Tr. at 663:10–664:3 (Gribble Cross 6.18.21); 1316:7–10 (Davies Direct 6.23.21).

330. The '358 Patent provides six example pharmaceutical formulations (Examples 21 to 26), none of which use apremilast or Example 12 as the active ingredient. Trial Tr. at

628:6–630:2, 664:5–13 (Gribble Cross 6.18.21); 1316:12–17 (Davies Direct 6.23.21); DTX-174 at 17:44–20:13.

331. Claim 16 is the only claim in the ’358 Patent that claims specific compounds (14 specific compounds), and it does not include Example 12. Trial Tr. at 664:14–23 (Gribble Cross 6.18.21); 1316:20–1317:1 (Davies Direct 6.23.21); DTX-174 at cl. 16.

332. The POSA would not have known whether Example 12 possessed the best potency by just looking at its structure; it could be the best among the 17 example compounds; it could be the worst. Trial Tr. at 665:6–11 (Gribble Cross 6.18.21).

333. The POSA would not have known whether Example 12 had the largest therapeutic window among the 17 example compounds just by looking at its structure. Trial Tr. at 666:21–24 (Gribble Cross 6.18.21).

2. The ’358 Patent does not disclose apremilast.[6]

a) Stereomerically pure apremilast and Example 12 are distinct compounds.

334. The ’358 Patent does not disclose stereomerically pure apremilast. Trial Tr. at 1388:24–25, 1389:12–13 (Davies Direct 6.23.21).

335. While the ’358 Patent includes Example 12, Example 12 discloses a racemate. Trial Tr. at 591:24–592:2 (Gribble Direct 6.18.21) (“Q. Now, when the person of skill in the

[6] In support of their anticipation defense for the ’638 Patent, Defendants sought to introduce evidence and expert testimony from Dr. Gribble regarding certain statements Celgene made to the European Patent Office in connection with the prosecution of a European patent, and Amgen conditionally offered rebuttal testimony from an expert in European Patent Office law and patent prosecution, Mr. Christopher Mercer. But Defendants’ evidence and testimony on this score has been excluded or stricken and Mr. Mercer’s testimony and documents introduced therein have been withdrawn, *see* ECF No. 465 at 2, 4 & n.1, and therefore neither the excluded evidence and stricken testimony nor the withdrawn testimony of Mr. Mercer will be addressed. To the extent Defendants argue a theory based on European Patent 1752148 (EP ’148), they have not established a way in which EP ’148 would be relevant to the ’638 Patent. *Cf. In re Larsen*, 292 F.2d 531, 533 (C.C.P.A. 1961) (“We have repeatedly held that, in view of the differences between foreign patent laws and those of the United States, the allowance of patent claims in foreign countries is not pertinent to the question whether similar claims should be allowed here.”).

art reads Example 12, do they immediately know that Example 12 is necessarily a racemate? A. Yes, they do."); 624:12–13 (Gribble Cross 6.18.21); 1315:8–25 (Davies Direct 6.23.21); *see* DTX-174 at 14:34–55.

336. The POSA would know from the synthesis described in Example 12 that Example 12 would be a racemate. Trial Tr. 1315:20–25 (Davies Direct 6.23.21); 592:5–9 (Gribble Direct 6.18.21).

337. In contrast, the Asserted Claims of the '638 Patent require *stereomerically pure apremilast*, an enantiomer. JSF ¶¶ 26–31 (ECF No. 422); Trial Tr. at 1298:24–1299:4, 1335:22–1336:1 (Davies Direct 6.23.21).

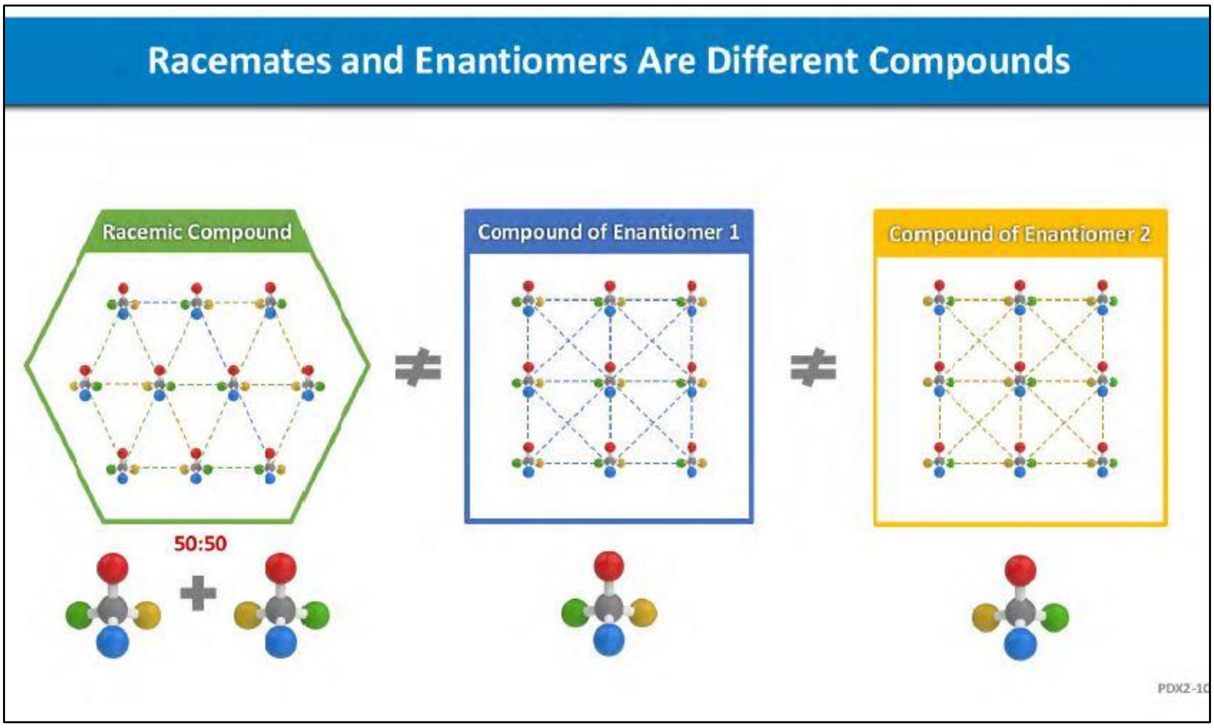
338. Stereomerically pure enantiomers are different compounds from their corresponding racemates. Trial Tr. at 90:19–22, 94:17–21 (Davies Direct 6.14.21); 1335:22–1336:2 (Davies Direct 6.23.21). Example 12 and stereomerically pure apremilast are two different compounds. Trial Tr. at 1335:22–1336:1, 1379:3–5 (Davies Direct 6.23.21).

339. The Chemical Abstracts Service, a division of the American Chemical Society, catalogs all known compounds in a searchable database, assigning each individual chemical compound a unique number. Trial Tr. at 1379:19–1380:9 (Davies Direct 6.23.21). The Chemical Abstracts Service formally recognizes enantiomers and racemates as different compounds. Trial Tr. at 1379:19–1380:9 (Davies Direct 6.23.21); 644:2–7 (Gribble Cross 6.18.21). Apremilast, an S-enantiomer, has a different Chemical Abstracts Service ("CAS") number (608141-41-9) than its R-enantiomer. The compound described in Example 12 of the '358 Patent, a racemate, has a different CAS number (253168-86-4) than both apremilast (the S-enantiomer) and the R-enantiomer of apremilast (608141-44-2). Trial Tr. at 1380:3–16 (Davies Direct 6.23.21); PTX-817; PTX-1174; PTX-1175.

340. The reason why racemates and enantiomers are different is in part due to the different intermolecular forces. Intermolecular forces as between two different enantiomers in

a racemate are different from the intermolecular forces as between the same enantiomers. Trial Tr. at 94:22–95:13 (Davies Direct 6.14.21); 1336:17–1337:15 (Davies Direct 6.23.21).

341. Exemplary differences in intermolecular forces as between enantiomers and racemates are illustrated in the following demonstrative, PDX2-10, used with Dr. Davies's testimony. The blue dashed lines represent the intermolecular forces between the molecules of one enantiomer and the yellow dashed lines represent the intermolecular forces between the molecules of the other enantiomer. As shown in the green hexagon, the racemic compound has interactions between two similar enantiomer molecules as well as interactions between molecules that are different enantiomers. It is these different intermolecular forces, or interactions, that make up the physical properties of the different compounds. Trial Tr. at 94:17–95:13 (Davies Direct 6.14.21).



b) Stereomerically pure apremilast is not separated, identified, and characterized in the '358 Patent.

342. Stereomerically pure apremilast is not separated, identified and characterized in the '358 Patent. PF ¶¶ 343–67.

343. The ’358 Patent does not disclose any individual enantiomers or isomers, at any level of stereomeric purity. Trial Tr. at 1382:20–23 (Davies Direct 6.23.21); 621:24–622:2 (Gribble Cross 6.18.21) (“A. They’ve not been separated in the ’358. That is correct.”).

344. The ’358 Patent only discloses racemates. Trial Tr. at 1382:15–19 (Davies Direct 6.23.21).

345. Neither enantiomer of the racemate described in Example 12 of the ’358 Patent is identified in the ’358 Patent. Trial Tr. at 1380:19–21 (Davies Direct 6.23.21).

346. The ’358 Patent does not include any specific mention of apremilast. Trial Tr. at 624:23–25 (Gribble Cross 6.18.21). Neither is the chemical structure or chemical name for apremilast explicitly set out in the ’358 Patent. Trial Tr. at 625:1–5, 625:13–16 (Gribble Cross 6.18.21).

347. There is no optical rotation data provided in the ’358 Patent. Trial Tr. at 626:8–10 (Gribble Cross 6.18.21).

348. Claim 1 of the ’358 Patent covers billions of compounds, of which apremilast is one of the billions. Trial Tr. at 598:5–599:4 (Gribble Direct 6.18.21); 664:14–23 (Gribble Cross 6.18.21); 1492:12–16, 1492:22–25 (Davies Redirect 6.23.21).

349. Example 12 in combination with the ’358 Patent’s statement that “[t]he compounds of Formula I possess a center of chirality and can exist as optical isomers…[t]he racemates can be used as such or can be separated into their individual isomers…,” DTX-174 at 8:63–9:12, does not disclose stereomerically pure apremilast. Trial Tr. at 1378:18–21 (Davies Direct 6.23.21). This statement applies generally to all compounds with a center of chirality, including the billions of compounds of Formula I. Trial Tr. at 620:6–22 (Gribble Cross 6.18.21).

350. Before the ’358 Patent, the POSA would have known that compounds with a center of chirality could exist as optical isomers. Trial Tr. at 621:3–621:6 (Gribble Cross 6.18.21); 1379:12–16 (Davies Direct 6.23.21).

351. Even without the ’358 Patent’s statement that “[t]he compounds of Formula I possess a center of chirality and can exist as optical isomers,” DTX-174 at 8:63–67, the POSA would have known that the compounds of Formula I possess a center of chirality and could exist as optical isomers. Trial Tr. at 621:7–9 (Gribble Cross 6.18.21).

352. Dr. Gribble testified that his opinions regarding the purported disclosure of the ’358 Patent with respect to apremilast would be the same whether or not the ’358 Patent stated that “[t]he compounds of Formula I possess a center of chirality and can exist as optical isomers,” DTX-174 at 8:63–67; Trial Tr. at 621:15–18 (Gribble Cross 6.18.21).

353. The ’358 Patent’s statement that “[t]he racemates can be used as such or can be separated into their individual isomers…,” DTX-174 at 8:63–9:12, applies generally to the billions of compounds in Formula I, and generally to any racemate, and is not specific to the ’358 Patent. Trial Tr. at 1378:18–1379:2 (Davies Direct 6.23.21); 621:20–622:2 (Gribble Cross 6.18.21). This statement would not have told the POSA anything that the POSA did not already know by October 1998; the POSA would have known that there are general methods by which one could try to separate enantiomers. Trial Tr. at 1379:6–11 (Davies Direct 6.23.21).

354. The ’358 Patent provides no information or details about how any of the general routes for making enantiomers listed in the ’358 Patent could have been applied to the compound described in Example 12. Trial Tr. at 1362:11–15, 1381:12–20 (Davies Direct 6.23.21).

355. There is no information in the ’358 Patent that would suggest to the POSA that each enantiomer of the racemate described in Example 12 had been prepared in stereomerically pure form separate from the racemate. Trial Tr. at 1380:22–1381:2 (Davies Direct 6.23.21);

see Trial Tr. at 631:3–631:5 (Gribble Cross 6.18.21) ("[Apremilast] has not been separated in the '358 [patent].").

356. The '358 Patent does not provide a specific method for making stereomerically pure apremilast. Trial Tr. at 630:4–7 (Gribble Cross 6.18.21).

357. The POSA would not understand from the '358 Patent that either enantiomer of the racemate described in Example 12 had been characterized in the '358 Patent. Trial Tr. at 1381:3–7 (Davies Direct 6.23.21).

358. The '358 Patent does not provide any characterization data for apremilast. Trial Tr. at 625:1–3 (Gribble Cross 6.18.21).

359. There is no characterization data in the '358 Patent to show that apremilast is the (+) isomer. Trial Tr. at 626:11–13 (Gribble Cross 6.18.21).

360. There is no solubility data for apremilast in the '358 Patent. Trial Tr. at 626:16–18 (Gribble Cross 6.18.21).

361. There is no biological data provided for apremilast in the '358 Patent. Trial Tr. at 626:19–21 (Gribble Cross 6.18.21); *see also* PF ¶¶ 577–79.

362. The '358 Patent also does not disclose stereomerically pure apremilast in an optical purity of greater than about 97% by weight. Trial Tr. at 1382:9–19 (Davies Direct 6.23.21).

363. The '358 Patent's statement regarding "an optical purity of >95%" (DTX-174 at 8:63–9:12) refers to obtaining enantiomers by chiral salt formation. Trial Tr. at 1382:3–8 (Davies Direct 6.23.21).

364. The '358 Patent does not disclose any individual enantiomer or isomer of any compound of Formula I at any level of stereomeric purity. Trial Tr. at 1382:20–23 (Davies Direct 6.23.21).

365. As of the date the application leading to the ’358 Patent was filed, October 30, 1998, apremilast had not yet been synthesized. Trial Tr. at 144:2–3 (Schafer Direct 6.14.21); 1304:1–5 (Davies Direct 6.23.21) (observing that apremilast was synthesized by October 21, 1999); DTX-174; JTX-148.

366. In contrast to the information lacking in the ’358 Patent about apremilast, the ’638 Patent clearly identifies and characterizes apremilast, which is described as a stereomerically pure compound. Trial Tr. at 631:7–640:4 (Gribble Cross 6.18.21, citing PDX-Gribble 1); JTX-3.

367. The differences between the disclosures of the ’358 Patent and ’638 Patent are set forth in the following chart. Trial Tr. at 631:11–640:8 (Gribble Cross 6.18.21, citing PDX-Gribble 1) (“Q. Okay. There's nothing on this chart that you disagree with; is that right, sir? . . . THE WITNESS: I would agree with that, yes.”).

	Disclosure	’358 Patent		’638 Patent	
1	Specific mention of apremilast	YES	**NO**	**YES**	NO
2	Characterization of apremilast	YES	**NO**	**YES**	NO
3	• Chiral HPLC	YES	**NO**	**YES**	NO
4	• Optical rotation	YES	**NO**	**YES**	NO
5	• Data to show (+) rotation	YES	**NO**	**YES**	NO
6	• Solubility	YES	**NO**	**YES**	NO
7	Biological data for apremilast	YES	**NO**	**YES**	NO
8	• Potency (PDE4, TNF-alpha)	YES	**NO**	**YES**	NO
9	• Cellular assay	YES	**NO**	**YES**	NO
10	• PDE4 selectivity	YES	**NO**	**YES**	NO
11	• Therapeutic index (emesis)	YES	**NO**	**YES**	NO
12	• *In vivo* testing	YES	**NO**	**YES**	NO
13	Dosage form of apremilast	YES	**NO**	**YES**	NO
14	Method of making stereomerically pure apremilast	YES	**NO**	**YES**	NO
15	Apremilast separated or prepared	YES	**NO**	**YES**	NO

PDX-GRIBBLE-1

c) The ’358 Patent does not disclose pharmaceutical compositions comprising stereomerically pure apremilast.

368. The POSA also would not have understood the ’358 Patent to disclose stereomerically pure apremilast in a pharmaceutical composition suitable for oral use. Trial Tr. at 1383:2–6 (Davies Direct 6.23.21).

369. Statements in the ’358 Patent regarding “[o]ral dosage forms . . . containing from 1 to 100 mg of drug per unit dosage,” DTX-174 at 9:22–30, do not disclose the 10 to 200 mg dose range of apremilast recited in claim 6 of the ’638 Patent and claim 6 of the ’536 Patent. Trial Tr. at 1385:1–6 (Davies Direct 6.23.21).

370. There is no potency data for stereomerically pure apremilast in the ’358 Patent, so there is nothing to suggest what the dose range may be. Trial Tr. at 1385:8–19 (Davies Direct 6.23.21).

371. None of the example pharmaceutical compositions listed in the ’358 Patent are oral pharmaceutical compositions comprising 10 to 200 mg of stereomerically pure apremilast. *See* DTX-174 at 17:44–20:13.

d) The ’358 Patent does not inherently disclose stereomerically pure apremilast.

372. Example 12 does not inherently result in stereomerically pure apremilast because Example 12 and stereomerically pure apremilast are different compounds. Trial Tr. at 1384:16–23 (Davies Direct 6.23.21).

373. Stereomerically pure apremilast is substantially free of its minus isomer and cannot also be a racemate. Trial Tr. at 1384:16–23 (Davies Direct 6.23.21).

374. The compound described in Example 12 is a 50:50 mixture of two enantiomers and cannot be a stereomerically pure enantiomer. Trial Tr. at 1384:16–23 (Davies Direct 6.23.21).

375. Following Example 12 and the general guidance in columns 8 and 9 of the ’358 Patent, DTX-174 at 8:63–9:12, 14:34–55, for obtaining enantiomers would not always and necessarily produce stereomerically pure apremilast, if at all. Trial Tr. at 1383:7–16 (Davies Direct 6.23.21). The general guidance in columns 8 and 9 of the ’358 Patent does not necessarily suggest obtaining enantiomers at all, but states that “[t]he racemates can be used as such…” DTX-174 at 8:67–9:1.

376. The chiral acid salt separation route described in columns 8 and 9 of the ’358 Patent, DTX-174 at 8:63–9:12, is not applicable at all for obtaining stereomerically pure apremilast. Trial Tr. at 1383:17–21 (Davies Direct 6.23.21).

377. The chiral chromatography route described in columns 8 and 9 of the ’358 Patent, DTX-174 at 8:63–9:12, does not tell one anything about how to acquire the enantiomers of Example 12; one would have to do a lot of work and may never find a route. Trial Tr. at 1383:17–24 (Davies Direct 6.23.21).

378. For the preparation “in chiral form” route described in columns 8 and 9 of the ’358 Patent, DTX-174 at 8:63–9:12, one would not know whether it would be possible at all because racemization may occur even if one manages to find a route to start with. Trial Tr. at 1383:17–1384:3 (Davies Direct 6.23.21).

379. One would not have been able to predict what weight percentage of stereomerically pure apremilast could be obtained through any of the general routes described in columns 8 and 9 of the ’358 Patent, DTX-174 at 8:63–9:12, without actually trying to do the separation. Trial Tr. at 1384:4–13 (Davies Direct 6.23.21).

3. The ’358 Patent is not an enabling reference.

380. The POSA would not have been able to make stereomerically pure apremilast without undue experimentation, if at all, based on the disclosure of the ’358 Patent. Trial Tr. at 1385:23–1386:6 (Davies Direct 6.23.21).

381. The ’358 Patent provides only general routes for how one might go about trying to prepare or separate the enantiomers of a racemic compound. Trial Tr. at 1362:11–20 (Davies Direct 6.23.21); 629:25–630:3 (Gribble Cross 6.23.21) (“Q . . . You also agree that the ’358 Patent does not provide a specific method for making stereomerically pure apremilast, correct? A. It does not.”); 1405:15–17 (Davies Cross 6.18.21) (“Q. . . . Now, the ’358 Patent, Doctor, says to separate enantiomers from the racemate, right? A. It doesn’t say -- it suggests you could.”).

382. None of the general routes in the ’358 Patent are specific to any compound in the ’358 Patent. Trial Tr. at 1378:18–1379:2 (Davies Direct 6.23.21); 622:8–10 (Gribble Cross 6.18.21).

383. As of October of 1998, the date the application leading to the ’358 Patent was filed, the POSA would have already been aware of the general routes listed in the ’358 Patent for making enantiomers. Trial Tr. at 1379:6–11 (Davies Direct 6.23.21); 622:17–623:2 (Gribble Cross 6.23.21); DTX-174 at 8:63–9:12.

384. The POSA also would have been aware that making enantiomers was a difficult process based on trial-and-error experimentation. JTX-181 at JTX-181_8 (“Although an experienced investigator can develop a ‘feel’ for the resolution of a racemic mixture, in practice working out the experimental conditions is still a process of trial and error.”) (“Selection of a resolution system is still a matter of trial and error and some resolutions have defied solution after trying many different resolving agents and solvents.”); JTX-183 at JTX-183_10 (“As of now, an optical resolution carried out in the usual manner is an empirical process.”).

385. General routes for making a particular enantiomer of Example 12 could include chiral chromatography, and direct synthesis techniques beginning with a chiral or achiral starting material, such as asymmetric synthesis. Trial Tr. at 1350:15–1351:13 (Davies Direct 6.23.21).

386. The POSA would have known that the chiral acid salt separation route, one of the routes provided in the '358 Patent, would not work to separate the enantiomers of the racemate described in Example 12, because Example 12 is not a base. Trial Tr. at 1363:4–13 (Davies Direct 6.23.21); 1409:23–24 (Davies Cross 6.23.21) ("That's not correct because the -- the salt formation method will not work for Example 12."); 645:15–19 (Gribble Cross 6.18.21) ("Q. And, in fact, Example 12 is not amenable to the use of a chiral acid salt to isolate its enantiomers from the racemate; is that right? A. It is not an acid or not amine, not a base. So one cannot make a conventional acid-base salt with Example 12.").

387. None of the general routes for making enantiomers are more predictable than any other; the POSA would not be able to predict which, if any, of the general routes would work to get the desired product. Trial Tr. at 1351:14–21 (Davies Direct 6.23.21).

a) Asymmetric synthesis

388. Developing a synthetic scheme to make a specific enantiomer may take many months to develop, and if a particular step in the synthetic scheme fails, most of the time the POSA needs to start at the beginning. Trial Tr. at 1352:1–18 (Davies Direct 6.23.21). As the literature at the time noted, "[h]istorically, the efficiency of asymmetric synthesis has been capricious in terms of chemical and optical yield." JTX-180 at JTX-180_94.

389. For example, Dr. Davies explained that designing a successful synthetic scheme to make a colchicine derivative compound took a graduate student and an experienced post-doctoral researcher in his research group eight to nine months to develop and consisted of eight separate steps. Trial Tr. at 1352:3-9 (Davies Direct 6.23.21). Dr. Davies explained that one must optimize each step before moving on to the next, and many of those "side routes" never work out. *Id.* at 1352:10-12.

390. There are no general methods available in the literature to perform an asymmetric synthesis to obtain an enantiomer. Trial Tr. at 1365:3–13 (Davies Direct 6.23.21).

391. If the POSA wanted to prepare stereomerically pure apremilast using asymmetric synthesis, the POSA would have had to start from scratch and devise a new synthetic scheme specific to apremilast. Trial Tr. at 1365:3–13 (Davies Direct 6.23.21).

b) Chiral acid salt separation

392. Chiral acid salt resolution and crystallization, or chiral acid salt separation, involves adding a chiral acid to a solution of a racemic compound to form salts in the solution with both enantiomers. Trial Tr. at 1353:13–22 (Davies Direct 6.23.21).

393. To separate the enantiomers, a differential crystallization—where only one of the enantiomer salts crystallizes out of solution—is performed, which leaves behind one of the enantiomer salts in solution. Trial Tr. at 1353:13–1354:12 (Davies Direct 6.23.21).

394. It is very difficult to perform chiral acid salt resolution on a new compound that has never been crystallized before, because it is often very hard to get the enantiomer salts to crystallize at all, and it is even harder to get them to differentially crystallize. Trial Tr. at 1354:8–12 (Davies Direct 6.23.21).

395. There were a huge number of chiral salt options available for chiral acid salt separation in the 1999 to 2002 timeframe; even in 1976 there were well over one hundred potential acids to experiment with, and that number increased over time. Trial Tr. at 1354:15–22 (Davies Direct 6.23.21).

396. The POSA had many different solvent system options available as of 1999 for using in a chiral acid salt separation. Trial Tr. at 1354:25–1355:8 (Davies Direct 6.23.21).

397. In addition to single solvents, the POSA could have picked combinations of solvents to use with chiral acid salt separation. Trial Tr. at 1355:3–12 (Davies Direct 6.23.21).

398. The POSA could have also used gradients of solvents in a chiral acid salt separation, which is where the composition of the solvents is changed during the separation. Trial Tr. at 1354:25–1355:8 (Davies Direct 6.23.21).

399. Nothing is predictable in choosing a solvent system for chiral acid separation. Trial Tr. at 1355:3–12 (Davies Direct 6.23.21) ("Nothing is predictable. You have to try. Trial and error.").

400. There were a huge number of options and ways the POSA could use to try and get enantiomer salts to differentially crystallize. Trial Tr. at 1355:9–12 (Davies Direct 6.23.21).

401. To separate enantiomers in a racemate using chiral acid salt separation, the POSA would need to add an acid to a base. Trial Tr. at 1363:4–13 (Davies Direct 6.23.21).

402. The POSA would also need to consider many variables to find appropriate crystallization conditions for a chiral acid salt separation, including temperature, concentration, and solvent choice. Trial Tr. at 1355:17–25 (Davies Direct 6.23.21).

403. In a chiral acid salt separation, the chiral acid salt, solvent system, and crystallization conditions are all independent variables. Obtaining the desired differential crystallization requires finding some congruence of all of those effects. Trial Tr. at 1356:1–8 (Davies Direct 6.23.21).

404. Not all chiral compounds can be separated using chiral acid salt separation. Trial Tr. at 645:12–14 (Gribble Cross 6.18.21).

c) Chiral chromatography

405. Chiral chromatography is a technique for separating enantiomers of a racemate involving introducing the racemate into a column with a chiral stationary phase ("CSP"). Trial Tr. at 1356:13–20 (Davies Direct 6.23.21); 1444:11–12 (Davies Cross 6.23.21) ("Q. CSPs. What does that stand for, Doctor? A. Chiral stationary phases.").

406. Ideally, the CSP is able to recognize one of the two enantiomers and it will retain that enantiomer while the other enantiomer passes through the column, which allows for a separation of the two enantiomers. Trial Tr. at 1356:13–20 (Davies Direct); 584:22–585:19 (Gribble Direct 6.18.21).

407. Chiral chromatography is not a universal method or technique for preparing enantiomers. Trial Tr. at 1357:3–15 (Davies Direct 6.23.21) ("Q. Now, Dr. Gribble testified that in his opinion, chiral chromatography is by far the most sufficient, it's the most developed now and it's the most widely used. You can do it on a small scale or a very large scale. It's the universal technique now. Do you agree? A. I certainly don't agree with that. If I -- if I believe that, I'd -- I've wasted 50 years of my academic career looking for methods -- other methods than this that allow you to do separations of compounds. . . . This is by no means a universal method or panacea at all.").

408. Thousands of groups around the world spend their time trying to find methods of preparing enantiomers not involving chiral chromatography. Trial Tr. at 1357:3–15 (Davies Direct 6.23.21) ("There are -- there are thousands of groups today around the world who spend their entire time trying to find other methods to do it.").

409. In attempting to devise a chiral chromatography method for separating the enantiomers of the racemate described in Example 12 of the '358 Patent into its enantiomers, the POSA would have had to find a chiral column that was capable of separating the two enantiomers of Example 12, if such a column existed at all, and then hope to find experimental conditions that would allow for that separation. Trial Tr. at 1357:16–22 (Davies Direct 6.23.21).

410. The '358 Patent does not identify any particular columns for separating the individual isomers of any of the compounds of Formula I. DTX-174 at 8:67–9:3.

411. Over 50 columns, or chiral stationary phases ("CSPs"), were available by the early 1990s. Trial Tr. at 1358:2–6 (Davies Direct 6.23.21); JTX-180 at JTX-180_20.

412. The POSA would not have known whether any of the commercially available columns in the early 1990s would have worked to separate the enantiomers of the racemate described in Example 12 of the '358 Patent. Trial Tr. at 1358:2–6, 1358:22–24 (Davies Direct

6.23.21) ("So this is unpredictable. You don't know which of these, if any, is going to work for you, and you don't know what conditions.").

413. The POSA would need to find a column that had chiral recognition for the enantiomers of Example 12, that is, the POSA needed to find a column that would interact sufficiently differently as between the two enantiomers in order to hold back one enantiomer in the column long enough to allow for a sufficient separation. Trial Tr. at 1358:7–21 (Davies Direct 6.23.21).

414. The POSA would also need to find an appropriate solvent system for the chiral column to separate the enantiomers. Trial Tr. at 1359:6–19 (Davies Direct 6.23.21).

415. There were lots of possibilities of solvent systems that the POSA could choose to try and separate enantiomers in a chiral column. Trial Tr. at 1359:20–23 (Davies Direct 6.23.21).

416. The POSA had a range of solvents to choose from and could combine them in any combination to try and separate the enantiomers. Trial Tr. at 1359:10–13, 1359:20–23 (Davies Direct 6.23.21).

417. The POSA could also have a solvent gradient, which involves starting with one solvent and slowly changing it to one or more different solvents. Trial Tr. at 1359:13–17 (Davies Direct 6.23.21).

418. The POSA would also need to consider the temperature, pH of the solvent system, and flow rate of the mobile phase in developing a chiral chromatography route. Trial Tr. at 1360:1–10 (Davies Direct 6.23.21).

419. The various choices that the POSA needed to consider in developing a chiral column route—the column, the solvent, the temperature, the pH, and the flow rate—are essentially independent variables and the POSA would need to find just the right combination, to the extent one existed at all, to separate a racemate into its enantiomers. Trial Tr. at 1360:11–

16 (Davies Direct 6.23.21). The general routes listed in the '358 Patent for how one might go about trying to prepare or separate the enantiomers of a racemic compound do not identify any of these variables for any compound described in the '358 Patent. *See* DTX-174 at 8:63–9:12.

420. The POSA would not have known how to design a chiral chromatography separation route to make the enantiomers of the racemate described in Example 12 of the '358 Patent without substantial experimentation. Trial Tr. at 1360:17–24 (Davies Direct 6.23.21).

421. If the POSA wanted to try to make stereomerically pure apremilast by chiral chromatography, the POSA would begin by purchasing chiral chromatography columns and start to look at various solvents, solvent mixtures, and various conditions to see if they could get any separation. Trial Tr. at 1364:5–11 (Davies Direct 6.23.21).

422. The structure of the compound in Example 12 would have informed the POSA only as to what solvents could be used with that compound Trial Tr. at 1364:12–19 (Davies Direct 6.23.21).

423. The other variables, including the chiral chromatography column, temperature, pH of the solvent system, and flow rate of the mobile phase would all need to be determined through experimentation. Trial Tr. at 1364:12–19 (Davies Direct 6.23.21).

424. The POSA would have been concerned that certain chiral chromatography conditions could result in degradation of Example 12. Trial Tr. at 1364:20–1365:2 (Davies Direct 6.23.21).

425. Chiral chromatography was normally performed on an analytical scale, such that only enough material is obtained at the end of the separation to do a spectroscopic investigation of what is coming off of the column and get a ratio of enantiomers. Trial Tr. at 1361:2–10 (Davies Direct 6.23.21).

426. In order to collect more material, the separation must be performed in a larger, preparative scale column. Trial Tr. at 1356:21–1357:2, 1361:2–24 (Davies Direct 6.23.21).

427. It is cost-prohibitive to experiment and identify separation conditions in chiral column chromatography on the preparative scale, so separations are first optimized on an analytical scale. Trial Tr. at 1361:2–20 (Davies Direct 6.23.21).

428. A separation that is optimized at the analytical scale does not translate directly to the preparative scale. Trial Tr. at 1361:11–20 (Davies Direct 6.23.21).

429. Many fewer preparative scale columns were available in the 1999 to 2002 time frame as compared to analytical columns, which meant that the number and type of compounds the POSA would have been able to separate on a preparative scale was more restricted. Trial Tr. at 1361:25–1362:4 (Davies Direct 6.23.21); 1491:11–17 (Davies Cross 6.23.21).

430. The POSA would have very limited access to preparative scale chromatography equipment, if at all. Trial Tr. at 1362:5–7 (Davies Direct 6.23.21).

431. Even if a separation was optimized on the analytical scale, the POSA would not necessarily be able to translate that to a preparative scale column. Trial Tr. at 1361:11–20 (Davies Direct 6.23.21).

432. Preparing stereomerically pure apremilast using chiral acid salt separation, chiral chromatography, or asymmetric synthesis would likely take a long time and a huge amount of effort to be successful. Trial Tr. at 1365:14–20 (Davies Direct 6.23.21).

433. Dr. Davies performed a literature search to see if he could find any reference to the compound described in Example 12 and apremilast, as well as structural analogs, to see if it apremilast or anything similar had been separated into enantiomers in the prior art, and he did not find anything. Trial Tr. at 1363:17–22 (Davies Direct 6.23.21).

d) The *Wands* analysis

434. Dr. Gribble did not perform an analysis as to whether or not the ’358 Patent would have enabled the POSA to make apremilast. Trial Tr. at 641:14–21 (Gribble Cross 6.18.21).

435. Dr. Gribble did not analyze the *Wands* factors for determining whether the POSA would have been able to make stereomerically pure apremilast without undue experimentation. Trial Tr. at 641:22–24 (Gribble Cross 6.18.21) ("Q. Okay. Now, you also aren't aware of something called the Wands factors; is that right? A. I'm not sure what that means, what that is.").

436. The first *Wands* factor—the time and cost of any necessary experimentation—weighs in favor of undue experimentation. Trial Tr. at 1387:4–14 (Davies Direct 6.23.21).

437. The general routes for making enantiomers that are listed in the '358 Patent would have required substantial time to make stereomerically pure apremilast, if it were possible at all. Trial Tr. at 1387:4–14 (Davies Direct 6.23.21); PF ¶ 432; *see also* PF ¶¶ 380–431.

438. It is cost-prohibitive to experiment and identify separation conditions in chiral column chromatography on the preparative scale, so separations are first optimized on an analytical scale. Trial Tr. 1361:2–20 (Davies Direct 6.23.21).

439. The price of a single analytical column for chiral chromatography in 1998 was about $800 to $1,600. Trial Tr. 1387:9–14 (Davies Direct 6.23.21).

440. The price of a single preparative chiral column in 1998 was between $27,000 to more than $67,000. Trial Tr. at 1387:9–14 (Davies Direct 6.23.21).

441. The cost of experimentation for any of the general routes for enantiomer separation listed in the '358 Patent would have been substantial, which further weighs in favor of undue experimentation. Trial Tr. at 1387:9–14 (Davies Direct 6.23.21).

442. The second *Wands* factor—how routine any necessary experimentation is in the field—weighs in favor of undue experimentation. Trial Tr. at 1387:15–19 (Davies Direct 6.23.21).

443. Routine experimentation for preparing an enantiomer starts from a published method. Trial Tr. at 1387:15–19 (Davies Direct 6.23.21).

444. Without any guidance from a published method, the POSA would have had to resort to picking any technique that was available, which is a very large number, and engaging in trial-and-error experimentation. Trial Tr. at 1363:24–1364:4 (Davies Direct 6.23.21); PF ¶¶ 384–433.

445. There was no published method for making stereomerically pure apremilast in the prior art, which weighs in favor of undue experimentation. Trial Tr. at 1363:14–22, 1387:15–19 (Davies Direct 6.23.21).

446. The third *Wands* factor—whether the patent discloses specific working examples—weighs in favor of undue experimentation. Trial Tr. at 1387:22–25 (Davies Direct 6.23.21).

447. The '358 Patent does not provide any working examples for making stereomerically pure apremilast. Trial Tr. at 1387:22–25 (Davies Direct 6.23.21). The general routes listed in the '358 Patent, DTX-174 at 8:67–9:12, are not specific to making any enantiomer of any compound in the '358 Patent. Trial Tr. at 1378:18–1379:2 (Davies Direct); 622:8–10 (Gribble Cross 6.18.21).

448. The fourth *Wands* factor—the amount of guidance presented in the patent—weighs in favor of undue experimentation. Trial Tr. at 1388:1–4 (Davies Direct 6.23.21).

449. The '358 Patent does not provide any specific guidance in making stereomerically pure apremilast. Trial Tr. at 1388:1–4, 1381:12–20 (Davies Direct 6.23.21); 630:4–7 (Gribble Cross 6.18.21) (Q. . . . You also agree that the '358 patent does not provide a specific method for making stereomerically pure apremilast, correct? A. It does not.").

450. The ’358 Patent only provides general methods that the POSA might apply or try to apply to obtain enantiomers of any of the billions of compounds encompassed by Formula I of the ’358 Patent. Trial Tr. at 1381:12–20 (Davies Direct 6.23.21); DTX-174 at 8:63–9:12.

451. The fifth *Wands* factor—the nature and predictability of the field—weighs in favor of undue experimentation. Trial Tr. at 1388:5–8 (Davies Direct 6.23.21).

452. Preparation of enantiomers is highly unpredictable and only achieved through trial-and-error experimentation. Trial Tr. at 1388:5–8 (Davies Direct 6.23.21); PF ¶¶ 384, 387.

453. The sixth *Wands* factor—the level of ordinary skill in the field—weighs in favor of undue experimentation. Trial Tr. at 1388:10–12 (Davies Direct 6.23.21).

454. Even experts in the field rely on trial-and-error experimentation to separate enantiomers. Trial Tr. at 1388:10–12 (Davies Direct 6.23.21).

455. Dr. Davies is an expert in preparing enantiomers, to the extent such experts can exist. Trial Tr. at 1350:5–12 (Davies Direct 6.23.21).

456. Virtually the entirety of Dr. Davies’s academic career has been dedicated to projects to acquire or make single enantiomers. Trial Tr. at 1349:13–16 (Davies Direct 6.23.21).

457. Dr. Davies formed a company in 1992 called Oxford Asymmetry, which aimed to provide single enantiomer compounds to researchers and pharmaceutical companies. Trial Tr. at 1490:10–23 (Davies Direct 6.23.21). The company would never guarantee that they could produce a particular enantiomer, however. *Id.* This is because everyone understood that “there’s no guarantee that we’ll ever find a method or how long it would take.” *Id.*

458. Dr. Davies has often been unsuccessful in making an enantiomer, and he and his colleagues have been attempting to resolve a particular enantiomer for over two decades without success. Trial Tr. at 1349:20–1350:4 (Davies Direct 6.23.21).

459. The seventh *Wands* factor—the nature and scope of the disclosure—is neutral with regards to undue experimentation. Trial Tr. at 1388:13–17 (Davies Direct 6.23.21).

460. The ’358 Patent’s disclosure pertains to a racemate and general routes to obtain enantiomers potentially applicable to any compound of Formula I in the ’358 Patent. Trial Tr. at 1388:13–17 (Davies Direct 6.23.21).

e) The ’638 Composition Patent does not “admit” that stereomerically pure apremilast was enabled by the prior art.

461. The ’638 Patent states that apremilast can be isolated from its racemate by techniques known in the art—not that the POSA would have been able to make and use stereomerically pure apremilast without undue experimentation. PF ¶¶ 462–63.

462. The ’638 Patent provides that “Compound A [apremilast] can be isolated from the racemic compound by techniques known in the art. Examples include, but are not limited to the formation of chiral salts and the use of chiral or high performance liquid chromatography “HPLC” and the formation and crystallization of chiral salts. [citing references].” JTX-3 at 9:13–24. This statement in the ’638 Patent is not an indication that isolation of apremilast by techniques known in the art was within the skill of the POSA. Trial Tr. at 1467:24–1468:5 (Davies Cross 6.23.21). Much like the general techniques in the ’358 Patent, the techniques known in the art that are listed in the ’638 Patent are general. Trial Tr. at 1468:6–7 (Davies Cross 6.23.21). That these techniques are known in the art is not the same as applying those techniques to a particular compound. Trial Tr. at 1468:2–7, 1468:12–20 (Davies Cross 6.23.21); *see also* Trial Tr. at 1473:12–22 (Davies Cross 6.23.21).

463. Eventually, stereomerically pure apremilast was isolated from the racemic compound by a general technique known in the art, but the “trick” is finding the specific conditions that would work for that particular compound. Trial Tr. at 1472:13–18 (Davies Cross 6.23.21).

464. The ’638 Patent provides a comprehensive method of making apremilast through a synthetic route, which is not a route of isolating apremilast from the racemic compound. JTX-3 at 21:6–22:29; Trial Tr. at 1484:1–19 (Davies Redirect 6.23.21); *see also* Trial Tr. at 1467:9–12; 1471:13–20 (Davies Cross 6.23.21).

465. The oath that the inventors of the ’638 Patent signed does not attest that the entire contents of the patent are accurate, but instead attests to the accuracy of statements made in the oath itself. Trial Tr. at 1481:2–1483:24 (Davies Redirect 6.23.21); JTX-16 at JTX-16_58-60 (stating that the inventor declares their “residence, post office address and citizenship,” that the inventor believes they are “the original, first and joint inventor of subject matter which is claimed and for which a patent is sought,” that the inventor has “reviewed and understand[s] the contents” of the application, that the inventor “acknowledge[s] the duty to disclose information known to me to be material to patentability,” and that the inventor is claiming certain benefits by filing the application).

D. Defendants Have Failed to Prove by Clear and Convincing Evidence that the ’638 Composition Patent Asserted Claims Are Invalid for Obviousness

466. Defendants did not adduce evidence sufficient to show by clear and convincing evidence that the ’638 Patent Asserted Claims are obvious. *See* PF ¶¶ 467–1010. Defendants assert two combinations that allegedly render the ’638 Patent Asserted Claims obvious: (1) the ’358 Patent and WO ’606 and (2) the ’358 Patent and Takeuchi. The ’638 Patent Asserted Claims would not have been obvious to the POSA over either combination. *See* PF ¶¶ 467–1010.

1. Defendants’ alleged prior art references

a) ’358 Patent

467. The facts concerning the ’358 Patent are incorporated here by reference. *See* PF ¶¶ 302–33.

b) WO ’606

468. Dr. Gribble did not identify WO ’606 on his own and it was provided to him by counsel. Trial Tr. at 671:2–671:8 (Gribble Cross 6.18.21).

469. The named inventors of WO ’606 are Drs. George Muller and Hon-Wah Man. DTX-159 at DTX-159_1; Trial Tr. at 671:11–13 (Gribble Cross 6.18.21); 1319:2–3 (Davies Direct 6.23.21).

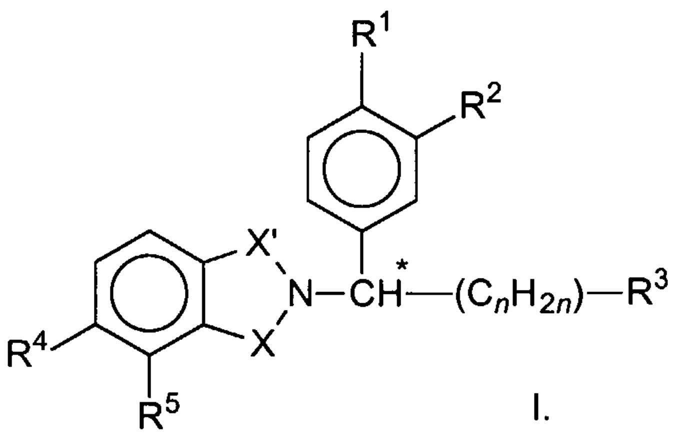
470. WO ’606 was filed on November 9, 2000 and claims priority to a US patent application dated November 12, 1999. DTX-159 at DTX-159_1; Trial Tr. at 1319:4–6 (Davies Direct 6.23.21).

471. WO ’606 was published on May 17, 2001. DTX-159 at DTX-159_1; Trial Tr. at 1319:7–8 (Davies Direct 6.23.21).

472. WO ’606 was published after the issuance of the ’358 Patent. Trial Tr. at 672:9–16 (Gribble Cross 6.23.21).

473. The priority application for WO ’606 was filed on November 12, 1999, approximately a year after the application leading to the ’358 Patent was filed (i.e., October 30, 1998). Trial Tr. at 1319:20–22 (Davies Direct 6.23.21).

474. WO ’606 discloses a class of compounds called Formula I, with the structure below. DTX-159 at 10:1–5.



I.

475. Formula I of WO ’606 encompasses billions of compounds. Trial Tr. at 1320:2–4 (Davies Direct 6.23.21); 672:21–23 (Gribble Cross 6.18.21) (“Q. Formula I in the WO ’606 application encompasses a very large number of compounds, right? A. It does. Like . . . the ’358 [Patent]”). WO ’606 contains the same general guidance on enantiomer separation as the ’358 Patent. *See* DTX-159 at 19:21–20:5; DTX-174 at 8:63–9:12.

476. WO ’606 claims isoindoline derivatives that have a thalimido group, which is also present in thalidomide. Trial Tr. at 1320:8–12 (Davies Direct 6.23.21); DTX-159 at DTX-159_1.

477. Example 12 of the ’358 Patent is covered by Formula I of WO ’606. Trial Tr. at 1320:16–19 (Davies Direct 6.23.21).

478. WO ’606 includes 78 examples; Example 12 of the ’358 Patent is not one of example compounds of WO ’606 and is not used in any of the example pharmaceutical compositions of WO ’606. DTX-159 at DTX-159_25–85; Trial Tr. at 1320:20–22 (Davies Direct 6.23.21).

479. WO ’606 includes no biological data for any of its compounds. Trial Tr. at 676:13–21 (Gribble Cross 6.18.21); 1320:5–7 (Davies Direct 6.23.21).

480. WO ’606 states that the invention “pertains to non-polypeptide isoindoline derivatives that decrease the levels of tumor necrosis factor alpha (TNFα) and inhibit phosphodiesterases (PDEs), particularly PDE 4 and PDE 3, and to the treatment of disease states mediated thereby.” DTX-159 at 1:6–9.

481. The POSA would not have expected that every single one of the compounds of WO ’606 inhibits PDE3 or PDE4. Trial Tr. at 676:22–25 (Gribble Cross 6.18.21).

482. WO ’606 explains that the structure of Example 12 of the ’358 Patent is not preferred. Trial Tr. at 1321:3–1322:2 (Davies Direct 6.23.21); 677:17–20 (Gribble Cross 6.18.21).

c) Takeuchi

483. The compounds in Takeuchi are "close structural mimics" of thalidomide and are not phenethylsulfones, like the compounds of the '358 Patent. Trial Tr. at 669:10–12 (Gribble Cross 6.18.21); DTX-174 at DTX-174_1.

484. Takeuchi et al. conducted the study to "elucidate the mechanism for the teratogenicity of [thalidomide] and to determine if pure enantiomers can lead to safe thalidomide-based drugs." DTX-168 at DTX-168_3.

485. Takeuchi does not describe any compound of the '358 Patent. Trial Tr. at 1322:18–20 (Davies Direct 6.23.21); 669:13–17 (Gribble Cross 6.18.21).

486. Example 12 of the '358 Patent is not described anywhere in Takeuchi. Trial Tr. at 1322:15–17 (Davies Direct 6.23.21).

487. Takeuchi discloses a particular method to separate the enantiomers from the racemate, 3-fluorothalidomide. DTX-168 at DTX-168_2. This method is specific to 3-fluorothalidomide, and does not teach the POSA how to make the enantiomers of Example 12 of the '358 Patent. Trial Tr. at 1325:15–19 (Davies Direct 6.23.21).

488. Takeuchi provides no information about PDE4 inhibition. Trial Tr. at 1324:12–14 (Davies Direct 6.23.21).

489. While Takeuchi reports that the S-isomer of 3-fluorothalidomide was found to be more active than the R-isomer, "the differences in the activities between the two may not be significant," and further studies were needed. DTX-168 at DTX-168_3; Trial Tr. at 1322:21–1324:11 (Davies Direct 6.23.21).

490. The enantiomers of 3-fluorothalidomide were separated using chiral HPLC, which normally is not a method used to collect sufficient quantities to do animal studies. Trial Tr. at 1325:1–14 (Davies Direct 6.23.21).

491. Takeuchi notes that the teratogenicity of its compounds "has not been measured yet because sufficient enantiomerically pure [compound] has not yet been accumulated to permit animal experiments." DTX-168 at DTX-168_3; Trial Tr. at 1324:15–22 (Davies Direct 6.23.21).

2. The state of the art with respect to PDE4 inhibitors and thalidomide

a) History of PDE4 inhibitor development

492. The phosphodiesterases ("PDEs") are a superfamily of enzymes that exist in the human body, divided into eleven families from PDE1 to PDE11. Trial Tr. at 135:18–21 (Schafer Direct 6.14.21). PDE4 is a member of the phosphodiesterase family. Trial Tr. at 135:18–21 (Schafer Direct 6.14.21).

493. PDE4 was first discovered in the late 1980's. Trial Tr. at 201:23–25 (Knowles Direct 6.15.21).

494. PDE4 works inside the cells of the body to control inflammatory responses, particularly by decreasing cyclic-AMP levels inside the body's cells. Trial Tr. at 201:11–13 (Knowles Direct 6.15.21). Cyclic-AMP (cAMP) is an intracellular messenger that controls the activities of cells, including controlling inflammation. Trial Tr. at 201:16–20 (Knowles Direct 6.15.21). Inhibition of PDE4 reduces the activity of the PDE4 enzyme inside the cell, which leads to an increase in intracellular cAMP, ultimately resulting in a decrease in inflammation. Trial Tr. at 201:15–19 (Knowles Direct 6.15.21).

(1) Finding and testing a PDE4 inhibitor required multiple rounds of testing.

495. As of both October 1999 and March 2002, multiple rounds of screening tests were used by researchers in a "cascade" of testing to evaluate PDE4 inhibitor compounds: *in vitro* assays like enzyme assays, cellular assays, and *in vivo* animal models, as well as assessments of pharmacokinetics and physicochemical properties and chronic safety studies.

Trial Tr. at 202:19–23 (Knowles Direct 6.15.21). At that time, enzyme assays were often the first step used to identify potential PDE4 inhibitor compounds. Trial Tr. at 203:18–22 (Knowles Direct 6.15.21).

496. Enzyme assays can measure *in vitro* inhibition of PDE4, and are conducted by testing a compound in a test tube or plastic "microtiter" plate in a laboratory. Trial Tr. at 203:18–204:17 (Knowles Direct 6.15.21).

497. Enzyme assays are a relatively quick and inexpensive way to determine whether a compound has any PDE4 inhibition potential, and, if it does, a rough indication of the potency of that inhibition in an *in vitro* setting. Trial Tr. at 203:18–204:12 (Knowles Direct 6.15.21).

498. A PDE4 enzyme assay results in an IC_{50}, a value representing the dose that inhibits 50% of the PDE4 present in the assay. Trial Tr. at 204:7–10 (Knowles Direct 6.15.21). A lower IC_{50}, in general, suggests higher potency. Trial Tr. at 204:18–23 (Knowles Direct 6.15.21).

499. Identifying a compound that exhibits *in vitro* inhibition of PDE4, however, is only the first step in a lengthy evaluation process. Trial Tr. at 202:16–23, 203:18–22 (Knowles Direct 6.15.21). The next step after enzyme assays would be cellular assays, which involve testing a compound in cells in a test tube. Trial Tr. at 204:25–205:1 (Knowles Direct 6.15.21). Cellular assays are considered more indicative of a compound's behavior in animals than enzyme assays. Trial Tr. at 205:11–14 (Knowles Direct 6.15.21).

500. If a compound shows sufficient PDE4 inhibition potential in enzyme assays, it would then be tested subsequently in cellular assays, but successful performance in an enzyme screening assay is not necessarily predictive of performance in cells. Trial Tr. at 205:11–17 (Knowles Direct 6.15.21).

501. If a compound shows sufficient PDE4 inhibition potential in a cellular assay, the next step in the PDE4 inhibitor evaluation process would be testing the compound in animal

models. Trial Tr. at 205:23–206:2 (Knowles Direct 6.15.21). The species used in animal models to evaluate PDE4 inhibition include mice, rats, guinea pigs, dogs, monkeys, and ferrets. Trial Tr. at 206:13–15 (Knowles Direct 6.15.21). Pharmaceutical companies used animal models to evaluate different aspects of PDE4 inhibition using different models, including a variety of models that may help to assess PDE4 anti-inflammatory effects. Trial Tr. at 206:15–19 (Knowles Direct 6.15.21).

502. Testing in animal models may include measuring a compound's therapeutic index. Trial Tr. at 205:25–206:2 (Knowles Direct 6.15.21). A "therapeutic index" is the difference in dose for a drug between its efficacy and its safety or tolerability. Trial Tr. at 156:9–18 (Schafer Direct 6.14.21); Trial Tr. at 207:14–25 (Knowles Direct 6.15.21). The higher the therapeutic index, in general, the safer the compound. Trial Tr. at 207:21–22 (Knowles Direct 6.15.21).

503. An example of a therapeutic index calculation is given in Example 8 of the '638 Patent. JTX-3 at 29:21–40; *see also* JTX-7 at 29:1–19. Example 8 of the '638 Patent describes a ferret model wherein the therapeutic index value was determined by "dividing the threshold dose for inducing emetic episodes by the ED50 value for inhibiting the pulmonary neutrophilia." JTX-3 at 29:22–28; *see also* JTX-7 at 28:16–18. Pulmonary neutrophilia is an inflammatory effect. Trial Tr. at 235:25–236:3 (Knowles Direct 6.15.21).

504. An ED_{50} value describes the dose that is a 50% inhibition of the desired effect. Trial Tr. at 236:3–4 (Knowles Direct 6.15.21). A lower ED_{50}, in generally, suggests higher potency. Trial Tr. at 154:15–21 (Schafer Direct 6.14.21).

505. Although the POSA would consider a relatively high therapeutic index value in animal models promising, it does not guarantee that a compound is safe and effective in humans. Trial Tr. at 207:21–25 (Knowles Direct 6.15.21).

506. A "therapeutic window" is a closely related concept that describes the range of efficacious doses that do not induce undesired side effects in the same species. Trial Tr. at 208:11–17 (Knowles Direct 6.15.21).

507. *In vivo* animal testing, as well as the earlier *in vitro* enzyme and cellular assays, are all considered "pre-clinical" testing. Trial Tr. at 159:14–20 (Schafer Direct 6.14.21).

508. If a compound succeeds in animal models, the next step would be to perform further assessments of the compound's physicochemical properties and animal pharmacokinetics. Trial Tr. at 208:22–24 (Knowles Direct 6.15.21).

509. Assessment of a compound's physicochemical properties and animal pharmacokinetics entails looking at the properties of the compound in detail, including dosing animals with the compound and measuring the levels of the compound in the blood, to understand how it is handled in the body. Trial Tr. at 209:1–6 (Knowles Direct 6.15.21).

510. Finally, for the small number of compounds likely remaining after all of the previous steps, these compounds would still undergo chronic safety studies. Trial Tr. at 209:11–16 (Knowles Direct 6.15.21). Chronic safety studies entail repeated dosing in two different animal species to determine the highest doses that can be given without identifiable safety concerns. Trial Tr. at 209:11–16 (Knowles Direct 6.15.21).

511. PDE4 inhibitor compounds would only have proceeded to human clinical trials if it was successful in each of the steps in this "cascade" of testing. Trial Tr. at 202:19–23 (Knowles Direct 6.15.21). At each stage of testing, the vast majority of compounds fail the screening criteria. Trial Tr. at 210:4–7 (Knowles Direct 6.15.21).

(2) By 1999 and 2002, many companies had developed many compounds as PDE4 inhibitors.

512. Starting in the late 1980s, there was great interest in PDE4 as a therapeutic target because inhibiting PDE4 was known to reduce inflammation. Trial Tr. at 218:15–17 (Knowles Direct 6.15.21). Pharmaceutical companies had growing interest in developing PDE4 inhibitors

over the course of the 1990s, and by 1999, most pharmaceutical companies were interested in and doing some type of work involving PDE4 inhibitors. Trial Tr. at 202:4–7 (Knowles Direct 6.15.21).

513. PDE4 inhibition was viewed as "one of the most intensively studied therapeutic targets currently of interest to the pharmaceutical industry . . . ." JTX-137 at JTX-137_15.

514. The research and published literature on PDE4 inhibitors was very much focused on asthma and COPD, although other therapeutic uses such as treatment of rheumatoid arthritis, Crohn's disease, or ulcerative colitis were also considered. Trial Tr. at 137:9–12, 141:23–142:2 (Schafer Direct 6.14.21); JTX-142 at JTX-142_2.

515. Progress in the development of PDE4 inhibitor compounds and the latest advances were often summarized in literature review articles. *See, e.g.*, JTX-67; JTX-137; JTX-142; JTX-282; PTX-497. By October 1999 and March 2002, there were hundreds of compounds reported in the public literature as potential PDE4 inhibitor candidates. Trial Tr. at 221:3–8 (Knowles Direct 6.15.21).

516. As of October 1999 and March 2002, FDA had not approved any PDE4 inhibitor. Trial Tr. at 1667:11–16 (Knowles Direct 6.25.21).

517. As of October 1999 and March 2002, at least ten compounds were in clinical development with a reported structure. Trial Tr. at 213:17–215:17 (Knowles Direct 6.15.21).

518. As of October 1999 and March 2002, other named compounds were reported as in clinical development but without a disclosed structure, and many more compounds had been reported as in preclinical development. Trial Tr. at 214:8–19 (Knowles Direct 6.15.21).

519. As of October 1999 and March 2002, the compounds that were the most advanced in clinical development (i.e., Phase 3 clinical studies) were cilomilast and roflumilast. Trial Tr. at 1667:22–1668:11 (Knowles Direct 6.25.21). The data available on the discontinuation of the development of PDE4 inhibitor compounds at that time was often

incomplete or unavailable. Trial Tr. at 227:1–6 (Knowles Direct 6.15.21). PDE4 inhibitor compounds reported in earlier review articles are often discontinued without a discussion of why the program was discontinued, resulting in a "publication bias" between the actual state of the art of PDE4 inhibitor development in October 1999 and March 2002, and what the available literature reflects. Trial Tr. at 227:1–6 (Knowles Direct 6.15.21). PDE4 inhibitor compounds would only have ceased to be described in publicly available literature if they were discontinued, and such compounds would generally only have been discontinued because of shortcomings in the compound's properties. Trial Tr. at 228:9–14 (Knowles Direct 6.15.21).

b) Overview of thalidomide

520. Thalidomide was approved in Europe and elsewhere in the 1950s to treat morning sickness. Trial Tr. at 101:20–24 (Davies Direct 6.14.21); JTX-160 at JTX-160_1. Thalidomide is notorious for having caused "one of the worst episodes in medical history." JTX-66 at JTX-66_7; Trial Tr. at 101:20–24 (Davies Direct 6.14.21); 119:13–17 (Davies Cross 6.14.21); 130:20–131:1 (Schafer Direct 6.14.21); 1747:5–1748:6 (Alexis Direct 6.25.21); *see also* Trial Tr. at 526:4–8 (Rohane Deposition Designations 6.16.21) ("I think most people in the United States are familiar with thalidomide, to some degree."); 526:9–15 ("[thalidomide] resulted in – many birth defects until it was identified, and then it was no longer used except in very, very limited situations").

521. "Between 1957 and 1962, thalidomide caused severe birth defects in over 10,000 children. Almost any tissue/organ could be affected by thalidomide. . . . Infant mortality in babies born with severe thalidomide embryopathy [which refers to the wide range of damage and conditions that thalidomide exposure can cause] is as high as 40%, quite likely due to internal organ damage . . . . Furthermore, many babies with these malformations are likely to have died *in utero* and been miscarried or stillborn. The true numbers of babies affected by thalidomide will likely never be known." JTX-160 at JTX-160_3; PTX-560.

522. The tendency of a compound to cause birth defects is referred to as teratogenicity. Trial Tr. at 97:24–98:1 (Davies Direct 6.14.21); Trial Tr. at 1747:11–13 (Alexis Direct 6.25.21).

523. Following the thalidomide disaster, FDA and other regulatory authorities made their approval processes for drugs and associated clinical trials much more stringent. Trial Tr. at 101:25–102:4 (Davies Direct 6.14.21); 130:20–131:1 (Schafer Direct 6.14.21).

524. In 1998, Thalidomide was approved by the United States Food and Drug Administration ("FDA") for use in the United States to treat a particular form of leprosy—a very debilitating bacterial disease that causes skin lesions and affects other organs and the eyes. JTX-169 at JTX-169_8 ("THALOMID (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL)."); Trial Tr. at 103:12–21 (Davies Direct 6.14.21); Trial Tr. at 1748:12–18 (Alexis Direct 6.25.21).

525. FDA approved thalidomide for the treatment of a severe form of leprosy (ENL) in part because of the severity and debilitating nature of the disease and the lack of available treatment options. Trial Tr. at 103:12–21, 104:20–105:5 (Davies Direct 6.14.21); JTX-169 at JTX-169_8.

526. Given the seriousness of leprosy (ENL), even a toxic and teratogenic drug like thalidomide may have a risk/benefit profile that favors approval. Trial Tr. at 104:20–105:5 (Davies Direct 6.14.21).

527. For a less serious and non-life threatening disease than leprosy (ENL), like psoriasis, the risks of approving thalidomide for treatment would far outweigh any potential benefits. Trial Tr. at 104:20–105:5 (Davies Direct 6.14.21) ("Q. If thalidomide is so dangerous, do you have any understanding of why FDA approved it at all? A. Well, with all approvals by the FDA for a treatment of a disease, there is a risk benefit analysis. If -- in something like leprosy, if it's a severe form of leprosy and there's nothing really to treat that, then the risk --

the benefit it might give the patient outweighs the risk; you'll see the teratogenic effects. But if you're looking at something that isn't life threatening and terrible like leprosy, such as psoriasis, then that would be a different kettle of fish."); Trial Tr. at 1748:23–1749:2 (Alexis Direct 6.25.21).

528. The package insert for thalidomide contains a "black box warning"—the highest level warning that FDA can put on an approved drug—so that anybody taking thalidomide and the physicians who might be prescribing it are fully aware of thalidomide's potential dangers. Trial Tr. at 103:22–104:19 (Davies Direct 6.14.21); JTX-169 at JTX-169_1–4.

529. The black box warning for thalidomide explains that, among other things, that thalidomide should never be taken by a pregnant women or women who may become pregnant because it can cause severe birth defects or death of an unborn baby. Trial Tr. at 104:5–19 (Davies Direct 6.14.21); JTX-169 at JTX-169_2. Black box warnings are FDA's way of highlighting the safety risk that the given medication can have severe side effects. Trial Tr. at 937:23–938:1 (Gilmore Direct 6.21.21).

530. The black box warning for thalidomide further provides that thalidomide can only be prescribed under certain conditions due to thalidomide's toxicity. Trial Tr. at 103:22–104:19 (Davies Direct 6.14.21); JTX-169 at JTX-169_1–4. While thalidomide was approved in 1998, its distribution was subject to strict control, including a distribution program called STEPS (System for Thalidomide Education and Prescribing Safety). JTX-66 at JTX-66_3; JTX-169 at JTX-169_18–21; Trial Tr. at 781:14–24 (Page Cross 6.18.21). STEPS involved "comprehensive patient counseling, a cautionary message from thalidomide victims, a detailed consent form and a mandatory thalidomide survey form." JTX-66 at JTX-66_3; Trial Tr. at 781:14–24 (Page Cross 6.18.21). These distribution requirements apply to both men and women. *See* JTX-169 at JTX-169_3–4. There are also black box warnings directed at male patients taking thalidomide. JTX-169 at JTX-169_4. For example, thalidomide carries a black

box warning that male patients taking thalidomide could potentially expose a fetus to thalidomide should they engage in sexual intercourse with a woman of child-bearing potential and, thus, under such circumstances, should use birth control even if they have undergone a vasectomy. JTX-169 at JTX-169_4. In the section of the thalidomide label describing how the body processes the drug, the label states "[i]t is not known whether thalidomide is present in the ejaculate of males." JTX-169 at JTX-169_6.

531. The prescribing information of thalidomide also carried a warning for peripheral neuropathy, "a nerve damage that may be permanent" and "a common, potentially severe, side effect of treatment with thalidomide that may be irreversible." JTX-169 at JTX-169_9; Trial Tr. at 1327:13–17 (Davies Direct 6.23.21). The prescribing information of thalidomide warned that "[p]eripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short term use also exist." JTX-169 at JTX-169_9; Trial Tr. at 1327:21–1328:3 (Davies Direct 6.23.21).

532. Dr. Gilmore did not offer any testimony regarding apremilast's association with thalidomide, or the impact such association would have had on the POSA's motivation to use apremilast as a part of a method of treatment for psoriasis with a reasonable expectation of success.

533. As of 1999 or 2002, the mechanism of action for the teratogenicity of thalidomide was not known. Trial Tr. at 132:5–10 (Schafer Direct 6.14.21); 658:24–659:2 (Gribble Cross 6.18.21). At that time, it was not known which part of the thalidomide molecule was responsible for teratogenicity. Trial Tr. at 102:23–25 (Davies Direct 6.14.21).

534. Even as of 2015, the actual mechanism by which thalidomide causes birth defects was not fully understood. JTX-160 at JTX-160_7 ("How does thalidomide cause the severe and wide range of damage in the embryo? The short answer is that it is still not fully understood. Over 30 separate models/theories for thalidomide embryopathy have been

proposed over the past 50 years[.]"); Trial Tr. at 102:19–22 (Davies Direct 6.14.21); 132:5–14 (Schafer Direct 6.14.21).

535. Thalidomide is a racemate, meaning a 50/50 mixture of R- and S-enantiomers. Trial Tr. at 103:5–6 (Davies Direct 6.14.21).

536. While the S-enantiomer of thalidomide is generally considered to be the cause of teratogenicity, the R- and S-enantiomers are known to readily interconvert in the body. Trial Tr. at 105:6–106:15 (Davies Direct 6.14.21); JTX-160 at JTX-160_2.

537. The ability of the R- and S-enantiomers of thalidomide to readily interconvert is due to the structure of thalidomide, which has an acidic hydrogen at the chiral center. Trial Tr. at 108:2–4 (Davies Direct 6.14.21).

538. Because of the interconversion of the R- and S-enantiomers of thalidomide, it was very difficult to separate the teratogenic properties of thalidomide from the therapeutic properties. Trial Tr. at 98:2–5 (Davies Direct 6.14.21); JTX-160 at JTX-160_2.

3. The POSA, seeking to develop a PDE4 inhibitor, would have sought a compound with robust biological data, such as cilomilast or roflumilast, as a starting point, not a compound from the '358 Patent.

a) The POSA would have wanted a PDE4 inhibitor with the right combination of properties.

539. At the end of the drug discovery process, the POSA would want a PDE4 inhibitor with the right combination of properties, including potency, selectivity, tolerability, safety, and drug like properties (e.g., bioavailabilities). Trial Tr. at 1664:11–1665:11 (Knowles Direct 6.25.21).

540. As of October 1999 and March 2002, finding a PDE4 inhibitor that had sufficient potency, selectivity, safety, drug-like properties, and a sufficiently high therapeutic index therefore would have been a difficult process requiring a substantial amount of labor and skill. Trial Tr. at 210:8–20 (Knowles Direct 6.15.21).

541. As of October 1999 or March 2002, the POSA looking to develop a PDE4 inhibitor would focus on maintaining tolerability at an effective dose. Trial Tr. at 1664:4–8 (Knowles Direct 6.25.21).

542. Nausea and emesis were considered a class-wide problem for PDE4 inhibitors. Trial Tr. at 1665:20–1666:1 (Knowles Direct 6.25.21). JTX-67 at JTX-67_5–7 ("[T]he side effects most commonly associated with selective PDE4 inhibitors are nausea and emesis."; Trial Tr. at 777:17–21 (Page Cross 6.18.21).

543. As of 1999 or 2002, in developing a PDE4 inhibitor, the POSA would have been most concerned about the side effects of emesis (i.e., retching and vomiting) and nausea. Trial Tr. at 1665:12–19 (Knowles Direct 6.25.21).

544. As Defendants' expert Dr. Page admitted, the key to finding a PDE4 inhibitor with an improved therapeutic index was (and still is today) to find a non-emetic pharmacophore as the starting point. Trial Tr. at 771:2–15 (Page Cross 6.18.21).

545. The POSA could not have determined whether a compound has an emetic pharmacophore by just doing *in vitro* testing; instead, animal testing would have been necessary. Trial Tr. at 772:21–25 (Page Cross 6.18.21).

546. For example, Dr. Page was involved in developing a dual PDE3 and PDE4 inhibitor, RPL554, also called ensifentrine. Trial Tr. at 695:4–12 (Page Direct 6.18.21); 773:4–6 (Page Cross 6.18.21). Ensifentrine is an analog of trequinsin. Trial Tr. at 773:7–9 (Page Cross 6.18.21). Dr. Page chose trequinsin as the starting point for further development because trequinsin was non-emetic based on reported data from clinical trials. Trial Tr. at 774:23–775:5, 775:17–25 (Page Cross 6.18.21).

547. In seeking to develop a PDE4 inhibitor, the POSA would have turned to the compound with the most robust biological data. Trial Tr. at 1660:20–1661:5, 1666:5–17 (Knowles Direct 6.25.21) ("Q. And why would the POSA have been interested in compound

with robust biological data rather than, say, no data at all? A. In the absence of biological data, you have no means of assessing or judging or improving one particular characteristics. You'd have to resort to a Ouija board or a séance or something. That's not how science works. You need biological data to make decisions and improve analysis."); 1329:7–11 (Davies Direct 6.23.21) ("Q. And why would the POSA have wanted to see biological data before selecting a lead? A. Because that would, at least, tell the POSA that there was some hope, some activity in the area they were looking at rather than just stab in the dark for a random compound."), 1329:12–17.

548. The POSA would not have selected a lead compound for further development without any biological data. Trial Tr. at 1666:18–1667:1 (Knowles Direct 6.25.21) ("Q. Last week you testified that you worked in the field for, I believe, around 35 years, including a number of years specifically on PDE4 inhibitors. During that time, have you ever selected a compound as a starting point for further development for which there was no reported biological data? A. No, I've never done that. I've never even had a subordinate suggesting that to me. They would have got short-shrift."); 1328:25–1329:6 (Davies Direct 6.23.21).

549. As of 1999, the binding site of PDE4 or the crystal structure of PDE4 was not known, which limited researchers' understanding of how compounds would interact with the PDE4 enzyme. Trial Tr. at 1346:8–13 (Davies Direct 6.23.21).

550. Because the binding site of PDE4 and the crystal structure of PDE4 were unknown, as of October 1999 or March 2002, the POSA looking to choose a starting point to develop a new PDE4 inhibitor compound would have first looked to compounds that were most advanced in clinical development. Trial Tr. at 1666:5–1667:10 (Knowles Direct 6.25.21).

551. Compounds in clinical development would generally have more biological data in the public domain. Trial Tr. at 1667:2–6 (Knowles Direct 6.25.21).

552. As of 1999 or 2002, there was no FDA-approved selective PDE4 inhibitor in the market. Trial Tr. at 1667:11–16 (Knowles Direct 6.25.21).

b) The POSA would have selected cilomilast or roflumilast as the starting point for further development.

553. The POSA, looking for a PDE4 inhibitor as of October 1999 or March 2002 would have selected either cilomilast or roflumilast as the starting point for further development because they were the most advanced PDE4 inhibitors. *See* PF ¶¶ 554–68.

554. As of October 1999, cilomilast and roflumilast were the most advanced PDE4 inhibitors in clinical development, both were reported to be in Phase 3 clinical studies for COPD and asthma. Trial Tr. at 1667:22–1668:3 (Knowles Direct 6.25.21); JTX-67 at JTX-67_5; JTX-142 at JTX-142_4.

555. As of October 1999, preclinical PDE4 potency data were available for cilomilast: it was reported to be a moderately potent PDE4 inhibitor with an IC_{50} of about 100 nm. Trial Tr. at 1668:25–1669:13 (Knowles Direct 6.25.21); JTX-142 at JTX-142_4. As of October 1999, tolerability data were available for cilomilast: it was found to be well-tolerated at doses of 15 mg b.i.d in humans. Trial Tr. at 1669:18–1670:2 (Knowles Direct 6.25.21); JTX-142 at JTX-142_4. As of October 1999, data relating to drug-like properties were available for cilomilast: cilomilast was 100% bioavailable and had a plasma half-life of 8 h. Trial Tr. at 1670:25–1671:10 (Knowles Direct 6.25.21); JTX-142 at JTX-142_4.

556. As of October 1999, data relating to the efficacy of cilomilast in Phase 2 clinical studies were available: treatment twice per day with cilomilast led to significant benefits for both COPD and asthma. Trial Tr. at 1670:3–20 (Knowles Direct 6.25.21); JTX-142 at JTX-142_4.

557. As of October 1999, clinical data relating to the safety, efficacy, and tolerability of cilomilast in Phase 3 clinical studies were available: in a multi-center, placebo-controlled, double-blind randomized parallel group Phase 3 trial in over 300 asthmatics, significant

improvement was observed, following twice per day administration of 15 mg of cilomilast, and "all doses tested were safe and well-tolerated." Trial Tr. at 1671:11–1672:11 (Knowles Direct 6.25.21); JTX-67 at JTX-67_7.

558. The fact that cilomilast had been reported to be in Phase 3 clinical studies would have made it the compound of interest to the POSA, because to reach advanced clinical studies, the compound must have passed stringent safety, efficacy, and tolerability requirements. Trial Tr. at 1673:17–1674:6 (Knowles Direct 6.25.21).

559. In 1999 and 2002, cilomilast, also known as Ariflo, was considered the gold standard against which all other PDE4 inhibitors are compared. Trial Tr. at 233:6–13 (Knowles Direct 6.15.21); 233:23–234:6 (Knowles Direct 6.15.21); JTX-142 at JTX-142_4; JTX-282 at JTX-282_2.

560. In 1999, cilomilast was clearly established as the most significant PDE4 inhibitor in clinical development. Trial Tr. at 233:14–18 (Knowles Direct 6.15.21); JTX-142 at JTX-142_4.

561. As of October 1999, roflumilast was reported to be in advanced clinical development for COPD and asthma, likely in Phase 3 clinical studies. Trial Tr. at 1676:11–17 (Knowles Direct 6.25.21); JTX-142 at JTX-142_5.

562. The fact that roflumilast was in advanced clinical development would have made roflumilast of great interest to the POSA. Trial Tr. at 1676:18–21 (Knowles Direct 6.25.21).

563. As of October 1999, preclinical PDE4 potency data and animal data were available for roflumilast: roflumilast was reported to be "a relatively potent inhibitor of PDE4, with an IC_{50} of 3.5 nM and to be active in standard guinea-pig models of asthma." Trial Tr. at 1676:22–1677:12 (Knowles Direct 6.25.21); JTX-142 at JTX-142_5.

564. As of March 2002, cilomilast and roflumilast were still the most advanced in clinical development: both were in Phase 3 clinical studies for COPD and asthma. Trial Tr. at 1668:8–11 (Knowles Direct 6.25.21); JTX-282 at JTX-282_2.

565. As of March 2002, additional data were reported for cilomilast, including data on animal models relating to potency and tolerability. Trial Tr. at 1674:25–1675:25 (Knowles Direct 6.25.21); JTX-282 at JTX-282_2.

566. As of March 2002, additional information was available about roflumilast, including clinical trial data regarding the tolerability of roflumilast. Trial Tr. at 1678:18–1679:6 (Knowles Direct 6.25.21); JTX-282 at JTX-282_3 ("The first six month study in COPD patients examined the efficacy of roflumilast administered at either 250 µg b.i.d. or 500 µg once daily in 516 patients. Neither dosage regimen induced significantly more emesis than placebo and both were well-tolerated.").

567. As of March 2002, data on roflumilast's drug-like properties were reported, including data on bioavailability and half-life. Trial Tr. at 1679:7–19 (Knowles Direct 6.25.21); JTX-282 at JTX-282_3 ("Roflumilast has been shown to be well-absorbed in man, with excellent bioavailability (79%) and a plasma half-life (15.7 h) suitable for once daily dosing.").

568. Based on the available information as of 1999 or 2002, cilomilast or roflumilast would have been compounds of great interest to the POSA for further development. Trial Tr. at 1676:1–4, 1680:13–18 (Knowles Direct 6.25.21).

c) The POSA would have selected other compounds in clinical or pre-clinical development with disclosed structures and biological data.

569. Assuming the POSA had wanted to look beyond PDE4 inhibitors in Phase 3 clinical studies, the POSA would have looked at other compounds that were in clinical studies but not quite as advanced as cilomilast or roflumilast. Trial Tr. at 1680:21–1681:4 (Knowles Direct 6.25.21).

570. As of October 1999, among compounds with disclosed structures, at least three compounds were in Phase 2 clinical studies (CDC-801,[7] V-11294A, and atizoram) and at least five compounds were in Phase 1 clinical studies (CI-1018, T-440, YM-58997, D-22888, and arofylline). Trial Tr. at 1681:8–11, 1682:11–14 (Knowles Direct 6.25.21, referencing PDX4-12); JTX-67 at JTX-67_3–5; JTX-142 at JTX-142_4–5.

PDE4 Inhibitor Compounds as of October 1999

Preclinical Evaluation	Phase 1 Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Discontinued
AWD-12-281 (asthma and allergic rhinitis)	CI-1018 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Rolipram (depression)
RS-17597	T-440 (asthma)	V-11294A (asthma)	Roflumilast (COPD and asthma)	Filaminast (asthma)
Org-20241 (asthma)	YM-58997 (asthma)	Atizoram (atopic dermatitis)		Piclamilast (asthma)
	D-22888 (asthma)			CDP-840 (asthma)
	Arofylline (asthma)			D-4418 (asthma)
				Ro-201724 (psoriasis)

JTX-137 at 2 (rolipram), 6 (T-440), 7 (RS-17597)
JTX-67 at 3–5 (T-440, AWD-12-281), 5–7 (Ro-201724, filaminast, piclamilast, CDP-840, atizoram, D-4418, cilomilast, CI-1018, D-22888, YM-58997, arofylline), 8 (AWD-12-281), 11 (atizoram), 12 (Ro-201724)
JTX-142 at 4–5 (cilomilast, roflumilast, CDC-801, V-11294A)
PTX-497 at 6 (Org-20241)

PDX4-12

571. After compounds in clinical studies, the POSA would have looked to compounds in preclinical evaluation. Trial Tr. at 1681:12–15 (Knowles Direct 6.25.21).

572. As of October 1999, among compounds with disclosed structures, at least three were in preclinical evaluation (AWD-12-281, Rs-17579, and Org-20241). Trial Tr. at 1681:16–18; 1682:11–14 (Knowles Direct 6.25.21 referencing PDX4-12); JTX-137 at JTX-137_2; PTX-497 at PTX-497_6; JTX-67 at JTX-67_3.

573. As of March 2002, among compounds with disclosed structures, at least five compounds were in Phase 2 studies (CDC-801, BAY-19-8004, pumafentrine, cipamfylline,

[7] CDC-801 would have been of less interest, because it was a thalidomide analog. *See* PF ¶¶ 580–90.

and mesopram) and at least two compounds were in Phase 1 studies (CI-1044 and SCH-351591). Trial Tr. at 1681:25–1682:4; 1682:11–14 (Knowles Direct 6.25.21); PTX-497 at PTX-497_3; JTX-282 at JTX-282_2–4.

PDE4 Inhibitor Compounds as of March 2002

Phase I Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Additional Discontinued
SCH-351591 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Arofylline (asthma)
CI-1044 (COPD and asthma)	BAY-19-8004 (COPD and asthma)	Roflumilast (COPD and asthma)	Atizoram (asthma)
	Pumafentrine (asthma)		Tibenelast
	Cipamfylline (dermatitis)		CI-1018 (asthma)
	Mesopram (multiple sclerosis)		D-22888 (asthma)
			V-11294A (asthma)
			YM-976 (asthma)

PTX-497 at 3 (arofylline), 4 (CI-1018), 5 (atizoram, tibenelast), 6 (D-22888)
JTX-282 at 1 (V-11294A, YM-976), 2 (SCH-351591, CI-1044, cilomilast, roflumilast, BAY-19,8004, pumafentrine, CDC-801, cipamfylline, mesopram), 4 (BAY-19-8004)

PDX4-13

574. CDC-998 was identified in a Celgene reference as a SelCID that had entered Phase I clinical trials by late 2000. JTX-66 at JTX-66_6. The POSA would not have known the structure of CDC-998 as of March 2002. JTX-282 at JTX-282_2; Trial Tr. at 1699:6–10 (Knowles Direct 6.25.21) ("Q. Does Marriott 2001 provide a structure of CDC-998? A. No, it does not. Q. Does any other prior art that you've reviewed discuss CDC-998 and provide its structure? A. No."). Without knowing the structure of CDC-998, the POSA would not have been interested in selecting it as a lead compound for further development. Trial Tr. at 1699:11–15 (Knowles Direct 6.25.21).

575. The POSA would not have been interested in selecting a compound for further development for which no structure was disclosed in the prior art. Trial Tr. at 1682:15–18 (Knowles Direct 6.25.21).

576. Without knowing the structure, the POSA would have had no means to investigate further and make modifications. Trial Tr. at 1682:19–25 (Knowles Direct 6.25.21).

d) The POSA would not have selected any compound of the ’358 Patent for further development.

(1) The ’358 Patent compounds’ relationship to thalidomide, the lack of biological data, and the concern over degradation would have dissuaded the POSA from selecting any compound of the ’358 Patent.

577. The POSA would not have selected any compound of the ’358 Patent for further development as there is absolutely no biological data for any of the compounds of the ’358 Patent. Trial Tr. at 1683:10–15 (Knowles Direct 6.25.21).

578. That the POSA would not have selected a compound from the ’358 Patent was explained graphically by Dr. Knowles, who explained that, as of October 1999, compared to cilomilast and roflumilast, none of the compounds of the ’358 Patent, including Example 12, had any data on PDE4 potency, drug-like properties, or tolerability, or any preclinical data, or had any information regarding clinical studies. Trial Tr. at 1688:9–1689:10 (Knowles Direct 6.25.21) (referencing PDX13-9); JTX-142 at JTX-142_4–5 (discussing cilomilast (i.e., “Ariflo” or “SB-207499”) and roflumilast); JTX-67 at JTX-67_7 (discussing cilomilast (i.e., “SB207499”); DTX-174 (’358 Patent).

The POSA Would Have Selected a Lead Compound with Robust Biological Data as of October 1999 – Not One with No Biological Data

Data Available/ In Clinical Trials	Cilomilast	Roflumilast	'358 patent: Formula I Compounds	'358 patent: Example 12
PDE4 potency (IC_{50})	✓	✓	✗	✗
Drug-like properties (e.g., bioavailability)	✓	✗	✗	✗
Tolerability (e.g., emesis)	✓	✗	✗	✗
Preclinical (e.g., animal studies)	✓	✓	✗	✗
Phase I (safety, side effects in humans)	✓	✓	✗	✗
Phase II/III (efficacy in humans)	✓	✓	✗	✗

JTX-142 at 4-5 (cilomilast, roflumilast)
JTX-67 at 7 (cilomilast)
DTX-174 *passim*

PDX13-9

579. That the POSA would not have selected a compound from the '358 Patent was explained graphically by Dr. Knowles, who explained that, as of March 2002, compared to cilomilast and roflumilast, none of the compounds of the '358 Patent, including Example 12, had any data on PDE4 potency, drug-like properties, or tolerability, or any preclinical data, or had any information regarding clinical studies. Trial Tr. at 1689:11–1690:3 (Knowles Direct 6.25.21) (referencing PDX13-10); JTX-142 at JTX-142_4–5 (discussing cilomilast (i.e., "Ariflo" or "SB-207499") and roflumilast); JTX-67 at JTX-67_7 (discussing cilomilast (i.e., "SB207499"); DTX-174 ('358 Patent); JTX-282 at JTX-282_3 (discussing roflumilast).

The POSA Would Have Selected a Lead Compound with Robust Biological Data as of March 2002 – Not One with No Biological Data

Data Available/ In Clinical Trials	Cilomilast	Roflumilast	’358 patent: Formula I Compounds	’358 patent: Example 12
PDE4 potency (IC_{50})	✓	✓	✗	✗
Drug-like properties (e.g., bioavailability)	✓	✓	✗	✗
Tolerability (e.g., emesis)	✓	✓	✗	✗
Preclinical (e.g., animal studies)	✓	✓	✗	✗
Phase I (safety, side effects in humans)	✓	✓	✗	✗
Phase II/III (efficacy in humans)	✓	✓	✗	✗

JTX-142 at 4-5 (cilomilast, roflumilast)
JTX-67 at 7 (cilomilast)
JTX-282 at 3 (roflumilast)
DTX-174 *passim*

PDX13-10

580. The POSA would not have selected a thalidomide analog for a drug development program in 1999 or 2002, like the compounds of the ’358 Patent, because of the known toxicity associated with thalidomide, including teratogenicity and the possibility of causing peripheral neuropathy. Trial Tr. at 1326:20–24 (Davies Direct 6.23.21).

581. Although thalidomide was approved in 1998 for treating the erythema nodosum leprosum (“ENL”), a complication of leprosy, JTX-169 at JTX-169_8, the prescribing information of thalidomide carried a four-page “black-box warning” for embryo-fatal toxicity, the highest level of warning that FDA puts on approved drugs. JTX-169 at JTX-169_1–4; Trial Tr. at 1327:4–8 (Davies Direct 6.23.21).

582. The concerns and drawbacks of thalidomide are incorporated by reference. *See* PF ¶¶ 520–38.

583. The prescribing information of thalidomide also carried a warning for peripheral neuropathy, “nerve damage that may be permanent” and “a common, potentially severe, side

effect of treatment with thalidomide that may be irreversible." JTX-169 at JTX-169_9; *accord* Trial Tr. at 1327:13–20 (Davies Direct 6.23.21).

584. The prescribing information of thalidomide warned that "[p]eripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short term use also exist." JTX-169 at JTX-169_9; Trial Tr. at 1327:21–1328:3 (Davies Direct 6.23.21).

585. In part because of the peripheral neuropathy warning, the POSA would have been concerned about the chronic use of thalidomide. Trial Tr. at 1327:21–1328:9 (Davies Direct 6.23.21).

586. A POSA selecting a lead compound for further development to treat a chronic disease would thus have avoided thalidomide—or its analogs—due to this concern. Trial Tr. at 1328:4–9 (Davies Direct 6.23.21).

587. As of 1999 or 2002, Celgene was the only company investigating thalidomide analogs as potential PDE4 inhibitors. Trial Tr. at 1328:18–22 (Davies Direct 6.23.21).

588. That Celgene had published on thalidomide analogs showing certain *in vitro* test results would not have alleviated the POSA's concern about thalidomide analogs. Marriott 2001 notes that "no data concerning clinical efficacy [of thalidomide analogs] has yet been published. Furthermore, far more data are required concerning the mechanisms of action of these compounds and the cellular targets that characterise their activities. Similarly, safety concerns associated with thalidomide will have to be closely monitored during use of the analogues." JTX-66 at JTX-66_7; Trial Tr. at 660:1–16 (Gribble Cross 6.18.21). Marriott 2001 notes that thalidomide analogs maybe useful in a number of clinical conditions for which there is "little other treatment option." JTX-66 at JTX-66_3; *see also* JTX-66 at JTX-66_7; Trial Tr. at 660:17–20 (Gribble Cross 6.18.21). Marriott 2001 also does not provide sufficient data for

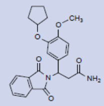
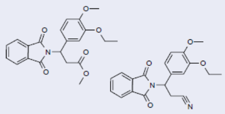
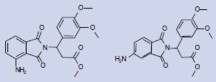
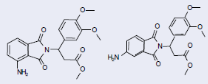
the POSA to appreciate anything about the toxicity of thalidomide analogs. *See* Trial Tr. at 1715:23–1716:7, 1716:22–1717:21 (Knowles Cross 6.25.21).

589. That the POSA would not have selected a thalidomide analog is further bolstered by the fact that Defendants' expert, Dr. Page, who has worked on 15-20 different PDE4 inhibitors and was working on PDE4 inhibitors in 1999, never worked on thalidomide analogs. Trial Tr. at 769:13–22 (Page Cross 6.18.21).

590. In addition to concerns about the relationship to thalidomide, the POSA would also have been concerned that the compounds of the '358 Patent may fragment into Michael Acceptors, which could occur in physiological conditions. Trial Tr. at 1331:8–25, 1332:14 (Davies Direct 6.23.21) ("Q. Under what condition might the sulfone compounds of the '358 Patent potentially turn into Michael Acceptors? A. Under either acid or basic conditions, both of which are present in the human body."), 1332:11–15; JTX-236 (describing the acidity of the protons next to the sulfone group, which would be one of the starting points for degradation). Michael Acceptors are a serious concern as even parts per million of Michael Acceptors can be carcinogenic. Trial Tr. at 1331:23–25, 1332:5–10 (Davies Direct 6.23.21).

(2) If the POSA considered a thalidomide analog, the POSA would have selected a PDE4 inhibitor thalidomide analog that had biological data.

591. The POSA would not have selected a thalidomide analog as a lead compound for further development. *See* PF ¶¶ 580–90. In the unlikely event that the POSA considered a thalidomide analog as a lead compound, the POSA would have started with a thalidomide analog with published data, including CDC-801, Compound Nos. 2b and 4b from Muller 1998, Compound Nos. 23 and 25 from Muller 1996, and Compound Nos. 21 and 23 from Muller 1997. Trial Tr. at 1329:20–1330:8 (Davies Direct 6.23.21); JTX-142 at JTX-142_5–6; JTX-69 at JTX-69_4; JTX-104 at JTX-104_2; JTX-105 at JTX-105_6.

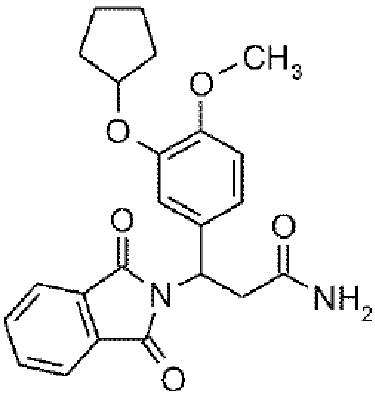
Compound (s)	Clinical Studies	PDE4 Inhibition IC_{50} (μM)	TNF-α Inhibition IC_{50} (μM)	Structure
CDC-801	• Phase II studies in Crohn's disease	• "a relatively weak inhibitor of both effects with IC_{50} values PDE4 (U937 cells) **1.1** μM…"	• "a relatively weak inhibitor of both effects with IC_{50} values…TNF-α production (monocytes) **2.5** μM"	
Compound nos. 2b, 4b (Muller 1998)	✗	• 2b: **0.23** • 4b: **0.13**	• 2b: **0.70** • 4b: **0.12**	
Compound nos. 23, 25 (Muller 1996)	✗	✗	• 23: **0.38** • 25: **0.45**	
Compound nos. 21, 23 (Muller 1997)	✗	✗	• 21: **0.38** • 23: **0.45**	

Norman 1999 (JTX-142), Muller 1998 (JTX-69), Muller 1996 (JTX-104), Muller 1997 (JTX-105)

PDX11-13

592. CDC-801 is a thalidomide analog. Trial Tr. at 1714:17–18 (Knowles Direct 6.25.21); JTX-142 at JTX-142_5.

593. The structure of CDC-801 was disclosed as of October 1999, as shown below. JTX-142 at JTX-142_3.



594. As of 1999, CDC-801 was in Phase 2 clinical studies and *in vitro* potency data for PDE4 and TNFα inhibition were available. JTX-142 at JTX-142_5–6; Trial Tr. at 1330:18–1331:1 (Davies Direct 6.23.21).

595. CDC-801 is a relatively weak inhibitor of PDE4 (IC_{50} 1.1 μm) and TNFα (IC_{50} 2.5 μM). JTX-142 at JTX-142_5–6.

596. Muller 1998 reports several thalidomide analogs with PDE4 and TNFα inhibitory activity, including compounds 2b and 4b. JTX-69 at JTX-69_4. Compound 2b has a

TNFα IC_{50} of 0.7 µM and PDE4 IC_{50} of 0.23 µM. JTX-69 at JTX-69_4. Compound 4b has a TNFα IC_{50} of 0.12 µM and PDE4 IC_{50} of 0.13 µM. JTX-69 at JTX-69_4.

597. The POSA would not have considered CDC-998 as a lead compound because its structure was not known. Trial Tr. at 1699:6–15 (Knowles Direct 6.25.21); JTX-282 at JTX-282_2; JTX-66.

(3) The POSA would not have selected one of the seventeen example compounds of the ’358 Patent as a starting point.

598. The POSA would not have turned to the 17 example compounds of the ’358 Patent because there is no data suggesting that any of the example compounds has any desirable properties. Trial Tr. at 1333:8–13 (Davies Direct 6.23.21); 1687:18–25 (Knowles Direct 6.25.21).

599. The POSA would not have turned to the 17 example compounds of the ’358 Patent, but if the POSA did, testing for different biological properties would be necessary, and activity data alone would not be sufficient. Trial Tr. at 1333:14–1334:1 (Davies Direct 6.23.21).

600. The POSA would not have tested all 17 example compounds of the ’358 Patent, but if one were to assume that the POSA did so, it would not have been “an obvious choice” for the POSA to pick Example 12 for further development. Trial Tr. at 1334:2–6 (Davies Direct 6.23.21).

601. Proprietary Celgene data, as tabulated below, shows that at least three other example compounds (Example 7, 10, and 16) have similar potency in terms of PDE4 inhibition as compared to Example 12. Trial Tr. at 1334:9–1335:3 (Davies Direct 6.23.21); JTX-184; PTX-850; PTX-851; PTX-853. The Celgene proprietary data also show that, “a lot of the [example] compounds” have similar potency in terms of TNFα inhibition as Example 12. Trial Tr. at 1486:24–1487:15 (Davies Redirect 6.23.21).

Table 2 - Proprietary Celgene PDE4 and TNFα Data for Example Compounds of the ’358 Patent

Ex. Compound	CC Number	PDE4 IC_{50} (µM)	TNFα IC_{50} (µM)
3	CC-5093	4.72	8.8
4	CC-6005	--	--
5	CC-6034	0.22	1.31
6	CC-6033	1.49	93.5
7	CC-6037	0.081	0.55
8	CC-6064	0.24	27.8
9	CC-6070	0.12	0.37
10	CC-7077	0.067	0.27
11	CC-7081	0.23	0.7
12	CC-7085	0.082	0.19
13	CC-7079	0.13	0.63
14	CC-7086	0.12	0.22
15	CC-7093	0.10	0.26
16	CC-7098	0.088	0.24
17	CC-8002	0.69	~0.3
19	CC-8070	0.26	1.51
20	CC-8071	0.13	0.61

602. The POSA would not have had access to the confidential Celgene data, but if the POSA did have such access, the POSA would not have had any reason to choose Example 12 over the other example compounds for further development. Trial Tr. at 1335:13–17 (Davies Direct 6.23.21).

603. While, numerically, among the seventeen compounds for which proprietary Celgene data is provided, Example 12 had the lowest TNFα IC_{50}, the POSA would not have selected Example 12 based on TNFα inhibition data alone. Defendants expert, Dr. Gribble testified that the POSA would be motivated to find a compound that inhibited PDE4. Trial Tr. at 607:10–608:4 (Gribble Direct 6.18.21) ("Possessing the pure enantiomers the POSA would have been motivated by the combined teachings of the '358 and the '606 to test both enantiomers for PDE4 inhibition and then reasonably have been expected that one or both of these enantiomers would inhibit PDE4."), 611:5–15 (similar, using combination involving Takeuchi). In addition, "a lot of the [example] compounds" have TNFα IC_{50} values in "more or less the same range" as Example 12. Trial Tr. at 1486:24–1487:15 (Davies Redirect 6.23.21).

(4) The POSA would not have made and tested each of the seventeen example compounds and all of their enantiomers.

604. Nor would the POSA have made and tested each of the seventeen example compounds and all of their enantiomers, because the POSA had no information about the racemic seventeen examples. Trial Tr. at 1366:17–1367:15 (Davies Direct 6.23.21).

605. It would have taken a huge amount of time and effort to synthesize and test each of the seventeen example compounds and all of their enantiomers. Trial Tr. at 1366:17–1367:15 (Davies Direct 6.23.21) ("The idea that a POSA would go off and make 17 racemates, resolve 17 compounds . . . each of which might take a huge amount of time and effort when they have no information about the -- the racemate; if they -- if they were working for me in academia [or] in one of my companies, they wouldn't be working for me much longer. The amount of effort and time and resources they would have wasted doing that would be unacceptable.").

e) Defendants' expert admitted that he did not conduct a lead compound analysis.

606. Dr. Gribble admitted that he did not analyze the prior art to determine what the lead compound would have been in developing a PDE4 inhibitor. Trial Tr. at 654:7–10 (Gribble Cross 6.18.21).

607. Dr. Gribble's sum total opinion as to why the POSA would have looked to the '358 Patent is that the POSA, "if he or she is interested in looking for compounds that would be potential inhibitors of PDE4 would have found the '358 patent . . . ." Trial Tr. at 603:5–10 (Gribble Direct 6.18.21).

608. The '358 Patent was provided to Dr. Gribble by Defendants' counsel. Trial Tr. at 618:21–619:8 (Gribble Cross 6.18.21).

609. Dr. Gribble's brief opinion as to why the POSA would have been motivated to arrive at apremilast using the '358 Patent is that "the POSA would go to one of the 17 examples [of the '358 Patent], look at those, and actually go ahead and synthesis those. That's not a big operation. And find activity and discover apremilast in Example 12." Trial Tr. at 603:21–604:9 (Gribble Direct 6.18.21).

4. The POSA would not have been motivated to modify either the thalidomide analogs with biological data or the 17 example compounds to make apremilast with a reasonable expectation of success.

610. The POSA would not have selected a thalidomide analog as a starting point for further development. However, had the POSA started with any of the thalidomide analogs with biological data available as of 1999 as a lead compound for further development, like CDC-801 or the compounds of Muller 1998, the POSA would not have been motivated to make apremilast with a reasonable expectation of success. Trial Tr. at 1331:2–5 (Davies Direct 6.23.21). Neither CDC-801 nor the compounds of Muller 1998 are encompassed by the '358 Patent. Trial Tr. at 1376:12–16 (Davies Direct 6.23.21).

611. Defendants have adduced no evidence as to how the POSA would have been motivated to modify CDC-801 in a way that would result in apremilast, or reasonably expect apremilast's combination of properties.

612. Defendants have adduced no evidence as to how the POSA would have been motivated to modify any of the other thalidomide analog compounds, in for example, Muller 1998 or Marriott 2001, in ways that would result in apremilast, or reasonably expect apremilast's combination of properties.

613. CDC-998 was identified in a Celgene reference as a SelCID that had entered Phase I clinical trials by late 2000. JTX-66 at JTX-66_6. Defendants have adduced no evidence that the POSA would have known of the structure of CDC-998.

614. Because Defendants cannot show that the POSA would have known of the structure of CDC-998, Defendants have adduced no evidence as to how the POSA would have been motivated to modify CDC-998 in a way that would result in apremilast, or reasonably expect apremilast's combination of properties.

615. Had the POSA made and tested each of the 17 example compounds for basic PDE4 and TNFα activity, the POSA would not have been motivated to modify, and eventually arrive at, apremilast, because even the confidential proprietary Celgene data showed a number of racemic compounds with similar PDE4 and TNFα inhibition data. Trial Tr. at 1367:7–1368:11 (Davies Direct 6.23.21); *see also* Trial Tr. at 1334:2–1335:3 (Davies Direct 6.23.21); 1486:24–1487:15 (Davies Redirect 6.23.21).

5. The POSA would not have been motivated to prepare the enantiomers of any of the example compounds, let alone specifically Example 12 of the '358 Patent.

a) Converting a racemate into a stereomerically pure enantiomer is a chemical modification.

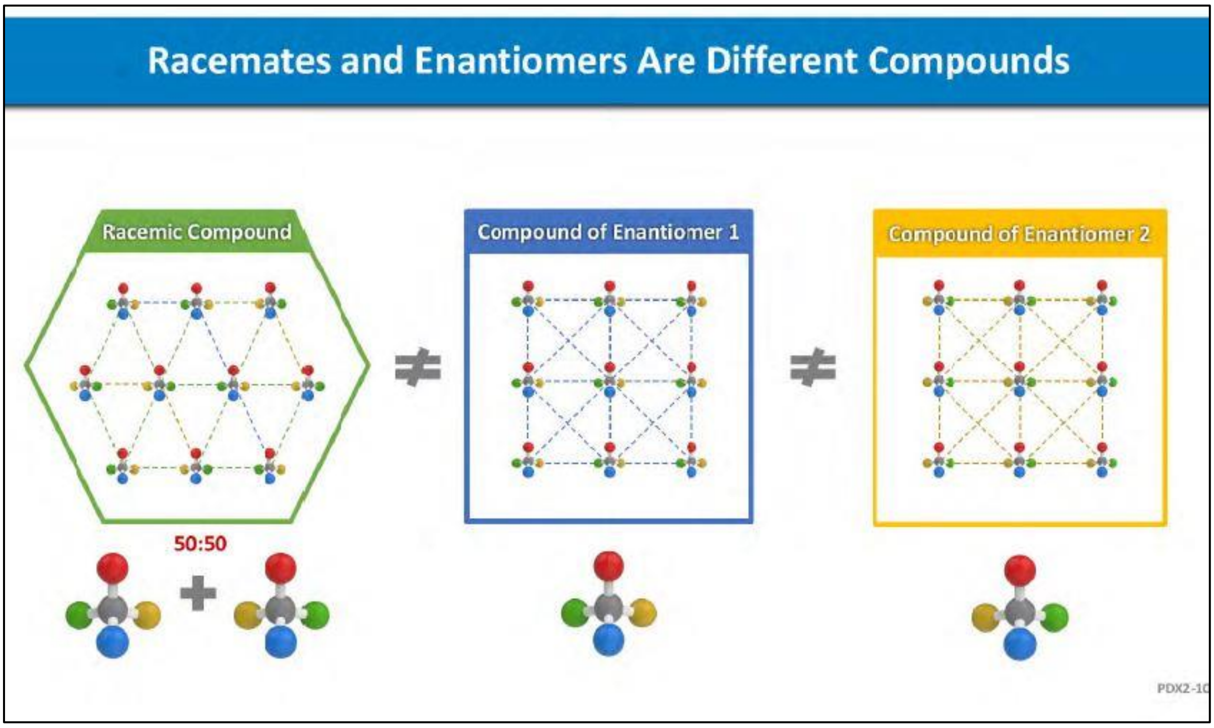
616. Chemical modification is the change of any one compound to another compound. Trial Tr. at 1335:19–21, 1336:3–9 (Davies Direct 6.23.21).

617. The racemic compound described in Example 12 of the ’358 Patent must be chemically modified to obtain stereomerically pure apremilast. Trial Tr. at 1335:22–1336:9 (Davies Direct 6.23.21).

618. Using chiral chromatography to separate enantiomers is a chemical modification that involves changing a racemic compound into a different compound, namely, a stereomerically pure enantiomer. Trial Tr. at 1337:16–22 (Davies Direct 6.23.21).

619. The intermolecular forces as between two different enantiomers in a racemate are different from the intermolecular forces as between the same enantiomers. Trial Tr. at 1336:14–1337:15 (Davies Direct 6.23.21).

620. Exemplary differences in intermolecular forces as between enantiomers and racemates are illustrated in, PDX2-10, used with Dr. Davies’s testimony. The blue dashed lines represent the intermolecular forces between the molecules of one enantiomer and the yellow dashed lines represent the intermolecular forces between the molecules of the other enantiomer. As shown in the green hexagon, the racemic compound has interactions between two similar enantiomers as well as interactions between molecules that are different enantiomers. It is these different intermolecular forces, or interactions, that make up the physical properties of the different compounds. Trial Tr. at 1336:14–1337:13 (Davies Direct 6.23.21).



621. Separating an enantiomer from a racemic compound involves altering the intermolecular bonding between individual molecules in a compound, which is a chemical modification. Trial Tr. at 1336:17–1337:15 (Davies Direct 6.23.21).

622. The POSA would have had to chemically modify Example 12 of the ’358 Patent to change it into stereomerically pure apremilast. Trial Tr. at 1335:22–1337:22 (Davies Direct 6.23.21).

623. The use of chiral chromatography to separate the enantiomers from Example 12 of the ’358 Patent is a chemical modification. Trial Tr. at 1337:16–22 (Davies Direct 6.23.21) (“Q. If you were to use chiral chromatography to separate the enantiomers from Example 12, would you consider that to be a chemical modification? A. Well, you’re changing a racemate, or a racemic compound, to a different compound, which is either Enantiomer 1 or Enantiomer 2. Changing one compound to another is a . . . chemical modification.”).

b) Although there may sometimes be motivation to separate an enantiomer, that is not the case with Example 12.

624. There are instances where the separation of enantiomers is appropriate, but the POSA would need data on the racemate first, to know if it is an active compound, to potentially have the motivation to separate the enantiomers. Trial Tr. at 1339:15–1340:7 (Davies Direct 6.23.21).

625. In 1992, the FDA issued guidance with respect to racemates and enantiomers and observed that "[w]hether separated enantiomers should be developed was largely an academic question because commercial separation of racemates was difficult." DTX-118 at DTX-118_1; *accord* DTX-119 at DTX-119_1.

626. The FDA guidance also noted that "the common practice of developing racemates has resulted in few recognized adverse consequences." DTX-118 at DTX-118_1–2; *accord* DTX-119 at DTX-119_2.

627. The FDA guidance further commented that "development of racemates may continue to be appropriate." DTX-118 at DTX-118_2; *accord* DTX-119 at DTX-119_2.

628. The FDA guidance invited discussion with drug manufacturers "concerning whether to pursue development of the racemate or the individual enantiomer." DTX-118 at DTX-118_2; *accord* DTX-119 at DTX-119_3.

629. Moreover, FDA's guidance regarding the need to "know[]" "the stereoisomeric composition of a drug with a chiral center" is not evidence of a motivation to always pursue enantiomers; as racemates are a 1:1 mixture of the two enantiomers, this is the one compound where the stereomeric composition is always known. Trial Tr. at 1448:12–1449:2 (Davies Cross 6.23.21); *see also* DTX-118 at DTX-118_2; DTX-119 at DTX-119_2.

630. If a racemate did not demonstrate any pharmacological activity, the POSA would not have moved forward to prepare the individual enantiomers. JTX-180 at JTX-

180_124 (“Should no pharmacological activity be demonstrated, the NCE [with a chiral center] is no longer considered a viable candidate drug.”).

631. If initial pharmacological testing shows adequate activity for the racemate, the next step would be to evaluate the compound in additional biological tests, as well as safety and toxicity studies. At this point, a decision may be made as to whether the racemate or the individual enantiomers should be tested. JTX-180 at JTX-180_124–125.

632. Because “time is a critical resource in drug development” and the preparation of single enantiomers can be difficult and time-consuming, it may be advantageous to move forward with testing the racemate only. JTX-180 at JTX-180_125.

633. The racemate v. enantiomer “debate” was very much alive in the 1990s. For example, on commentator argued that “for many marketed racemic drugs, such as the β-adrenoceptor antagonists, available evidence indicates that the therapeutically inactive enantiomer is not harmful, and that the patient would not benefit from receiving the pure active enantiomer.” JTX-180 at JTX-180_130.

c) The POSA would not have been motivated to acquire the enantiomers of Example 12.

634. The POSA would not have been motivated to acquire the enantiomers of Example 12 because there was no data suggesting that Example 12 had any activity. Trial Tr. at 1339:15–1340:7 (Davies Direct 6.23.21).

635. Based on the information available in the prior art, the POSA would not have reasonably expected any difference in biological properties between Example 12 and its enantiomers. Trial Tr. at 1342:15–23 (Davies Direct 6.23.21). It is possible that a racemate could have the same biological activity as its individual enantiomers. Trial Tr. at 668:13–16 (Gribble Cross 6.18.21); 96:14–97:1 (Davies Direct 6.15.21); 1344:23–1346:7 (Davies Direct 6.23.21).

636. That the POSA would not have reasonably expected any difference in biological properties between Example 12 and its enantiomers is illustrated by Compound 19 in Muller 1997, which is structurally related to Example 12 of the '358 Patent. Trial Tr. at 1341:3–6, 1341:22–1342:13 (Davies Direct 6.23.21) (explaining that Muller 1997 discusses thalidomide analogs and that both compound 19 of Muller 1997 and Example 12 of the '358 Patent have a thalimido group and the dialkoxyphenol group); *see also* JTX-105 at JTX-105_3.

637. Muller 1997 reports that the S- and R-enantiomers of compound 19 had similar dose-response curves as the racemate and both were able to completely inhibit TNFα. JTX-105 at JTX-105_6–7. In other words, the enantiomers of compound 19 of Muller 1997 had similar potency to each other in inhibiting TNFα, and did not show any difference from the racemate. Trial Tr. at 1341:10–1342:3 (Davies Direct 6.23.21).

638. There were no other examples of enantiomers of thalidomide analogs that contained the thalimido ring structure on the one hand and the dialkoxyphenol group on the other hand in the prior art as of 1999 or 2002. Trial Tr. at 1342:24–1343:3 (Davies Direct 6.23.21).

639. Nothing in the prior art, including the '358 Patent, would have told the POSA that the S-enantiomer or the (+) enantiomer of Example 12 of the '358 Patent had any desirable properties over Example 12. Trial Tr. at 667:19–668:7 (Gribble Cross 6.18.21).

640. The POSA would not know whether any enantiomers of a particular compound have superior properties as compared to the racemate until the individual enantiomers were isolated and tested. Trial Tr. at 668:8–12 (Gribble Cross 6.18.21).

641. The fact that Celgene advanced a racemate, CDC-801, into Phase 2 clinical studies by 1999 would have further suggested to the POSA that the enantiomers may not have any advantage over Example 12 itself. Trial Tr. at 1340:12–19 (Davies Direct 6.23.21).

642. That the POSA would not have been motivated to prepare the enantiomers of Example 12 is further supported by the real-life evidence of what the inventors did, which was to take CC-7085 into clinical studies in late 2000, after Celgene already had apremilast in hand. Trial Tr. at 1370:19–1371:18 (Davies Direct 6.23.21); 139:19–21 (Schafer Direct 6.14.21).

643. That the POSA would not have been motivated to prepare the enantiomers of Example 12 is further supported by the real-life evidence of what the inventors did: the inventors also did not prepare apremilast for over a year after first synthesizing and testing CC-7085. Trial Tr. at 144:4–8, 140:10–12 (Schafer Direct 6.14.21).

d) The POSA would have been motivated to make other structural modifications to Example 12.

644. Although the POSA would not have selected Example 12 as a starting point, if they had, the POSA would have then made structural modifications to Example 12 to try to obtain an improved compound. Trial Tr. at 1339:3–14, 1343:4–13 (Davies Direct 6.23.21).

645. If the POSA were motivated to modify Example 12, the POSA could have modified Example 12 in light of the structure of CDC-801, given the structure of CDC-801 was publicly available and it had entered Phase 2 clinical studies. Trial Tr. at 1343:16–24 (Davies Direct 6.23.21); JTX-142 at JTX-142_3, _5 (reporting the structure of CDC-801 and that it "is now undergoing Phase II studies").

646. Modifications of Example 12 based on the structure of CDC-801 would not have led to apremilast, but instead to different compounds. Trial Tr. at 1343:16–24 (Davies Direct 6.23.21) (describing how POSA may have changed Example 12 in light of CDC-801).

647. Dr. Gribble provided no evidence demonstrating that the POSA would have been motivated to select CDC-801 as a lead compound and modify it in a way to become apremilast, with a reasonable expectation of success.

648. If the POSA had been motivated to modify Example 12, the POSA could have modified Example 12 in light of the structure of compounds 2b and 4b of Muller 1998, given

their relatively high potency in inhibiting PDE4. Trial Tr. at 1344:2–9 (Davies Direct 6.23.21); JTX-69 at JTX-69_4 (reporting structure and potency data for compounds 2b and 4b).

649. Modifications of Example 12 based on the structures of compounds 2b and 4b of Muller 1998 would not have led to apremilast, but instead to different compounds. Trial Tr. at 1344:2–9 (Davies Direct 6.23.21) (describing how POSA may have changed Example 12 in light of Muller 1998 compounds 2b and 4b).

6. The POSA would not have reasonably expected to succeed in making apremilast.

650. For the reasons set forth above, with respect to the difficulties of making enantiomers, *see* PF ¶¶ 380–460, the POSA would not have had a reasonable expectation of success in actually making apremilast, as it would be a difficult and unpredictable process that likely would take a long time. Trial Tr. at 1349:2–12, 1365:14–20 (Davies Direct 6.23.21).

7. The POSA would not have reasonably expected to obtain the desirable properties of apremilast.

a) The POSA would have had no reasonable expectations about apremilast's properties.

651. Without any biological data for Example 12 of the '358 Patent, the POSA would not have reasonably expected any desirable properties, including potency, selectivity, safety, tolerability, and drug-like properties, in Example 12. Trial Tr. at 1344:10–15 (Davies Direct 6.23.21); 1690:4–15 (Knowles Direct 6.25.21).

652. As of 1999 or 2002, no data (e.g., PDE4 potency, safety, tolerability, selectivity, drug-like properties) were publicly available for any of the enantiomers of the example compounds of the '358 Patent. Trial Tr. at 1690:20–1691:6 (Knowles Direct 6.25.21).

653. Without data, the POSA would not have reasonably expected the enantiomers of Example 12 to have any desirable properties, including potency, selectivity, safety, tolerability, and drug-like properties. Trial Tr. at 1344:16–22, 1366:9–16 (Davies Direct 6.23.21); 1690:4–15, 1691:7–10 (Knowles Direct 6.25.21).

654. As of 1999 or 2002, it would have been a rarity for a PDE4 inhibitor to have the combination of right potency, selectivity, safety, tolerability, and drug-like properties. Trial Tr. at 1690:16–19 (Knowles Direct 6.25.21).

b) There was no data in the prior art that would have suggested that the S-enantiomer of Example 12 possessed desirable properties.

655. Dr. Gribble agreed that he had not seen anything in the prior art to suggest that the S-enantiomer or the plus enantiomer of Example 12 had any desirable properties over Example 12. Trial Tr. at 667:19–668:16 (Gribble Cross 6.18.21).

656. Dr. Gribble agreed that "there's no way to know in advance" which enantiomer of Example 12 is more potent. Trial Tr. at 605:4–9 (Gribble Direct 6.18.21); *accord* 667:19–668:16 (Gribble Cross 6.18.21).

657. Wnendt 1996 reports that for thalidomide and configuration-stable thalidomide-analogs, the S-enantiomer was more active in inhibiting TNFα than the R-enantiomer. JTX-239 at JTX-239_5; Trial Tr. at 661:10–18 (Gribble Cross 6.18.21).

658. Wnendt also reports that the S-enantiomers of the thalidomide-analogs studied had a higher activity in mediating sedation. JTX-239 at JTX-239_5; Trial Tr. at 661:19–662:1 (Gribble Cross 6.18.21). However, the teratogenicity also resided in the S-enantiomers compared to the respective R-enantiomers. JTX-239 at JTX-239_5; Trial Tr. at 661: 19–662:1 (Gribble Cross 6.18.21). Accordingly, Wnendt concluded that "[t]he congruent enantioselectivity towards the (S)-form in three different biological effects strongly suggests that with this class of compounds it will not be possible to separate the teratogenicity from the desired pharmacological properties just by employing the right configuration-stable enantiomer." JTX-239 at JTX-239_5.

659. Muller 1999 reports that compound 5a was a potent inhibitor of TNFα, but showed no activity in inhibiting PDE4. JTX-68 at JTX-68_4–5 ("These results strongly suggested that these compounds do not act by PDE4 inhibition.").

660. Muller 1999 reports that the S-enantiomer of its compound 5a was more active than the R-enantiomer of compound 5a. JTX-68 at JTX-68_4.

661. The POSA would not have reasonably expected the S-enantiomer of Example 12 would be more active than the R-enantiomer of Example 12 based on Muller 1999, Takeuchi, and Wnendt, because the compounds of Muller 1999, Takeuchi, and Wnendt are structurally different from Example 12 of the '358 Patent. Trial Tr. at 1488:8–17 (Davies Redirect 6.23.21).

662. The POSA would not reasonably have expected that the S-enantiomer of Example 12 would be more active than the R-enantiomer of Example 12 based on Muller 1999, Takeuchi, and Wnendt, because whether the "R" or "S" designation is used for the enantiomer of a particular compound does not relate to the use of "R" or "S" designation for a different compound: minor changes to the substituents of a compound could switch the R/S designation of that compound. Trial Tr. at 1488:18–1489:13 (Davies Redirect 6.23.21).

8. The POSA would not have been motivated to use apremilast or have had a reasonable expectation that it would have the properties that would make it suitable for use in a pharmaceutical composition.

663. Putting aside the issue of whether or not the POSA could successfully make apremilast, the POSA would not have had any data about apremilast. Trial Tr. at 1692:6–8 (Knowles Direct 6.25.21). The POSA would have had no knowledge of its potency, safety, tolerability, selectivity, or drug-like properties. Trial Tr. at 1692:9–19 (Knowles Direct 6.25.21).

664. Even assuming the POSA had apremilast in one hand and the ’358 Patent in the other, the POSA would not have been able to draw any conclusion about apremilast from the ’358 Patent. Trial Tr. at 1692:20–24 (Knowles Direct 6.25.21).

665. The POSA would not have been motivated to make a pharmaceutical composition suitable for use in humans comprising stereomerically pure apremilast with a reasonable expectation of success, given the complete absence of data about apremilast in the prior art and the POSA’s concern about apremilast’s connection to thalidomide. Trial Tr. at 1368:12–1369:4 (Davies Direct 6.23.21); 1691:16–25 (Knowles Direct 6.25.21).

9. Neither WO ’606 nor Takeuchi remedies the deficiencies of Defendants’ obviousness argument.

666. WO ’606 would not have motivated the POSA to select Example 12 of the ’358 Patent, at least because WO ’606 considers Example 12 to be not preferred. Trial Tr. at 1346:14–20 (Davies Direct 6.23.21).

667. WO ’606 does not teach the POSA anything about making enantiomers of Example 12 of the ’358 Patent. Trial Tr. at 1322:4–6 (Davies Direct 6.23.21).

668. WO ’606 does not remedy any of the deficiencies of the ’358 Patent. Trial Tr. at 1370:16–18 (Davies Direct 6.23.21).

669. Takeuchi would not have motivated the POSA to select Example 12 of the ’358 Patent, at least because it does not address PDE4 inhibition or Example 12. Trial Tr. at 1324:12–14, 1346:21–1347:1 (Davies Direct 6.23.21).

670. Takeuchi would not have motivated the POSA to make the enantiomers of Example 12. Trial Tr. at 1346:21–1347:1 (Davies Direct 6.23.21).

671. Takeuchi does not teach the POSA anything about making enantiomers of Example 12 of the ’358 Patent. Trial Tr. at 1325:15–19 (Davies Direct 6.23.21).

672. Takeuchi does not remedy any of the deficiencies of the ’358 Patent. Trial Tr. at 1370:16–18 (Davies Direct 6.23.21).

10. Objective indicia

a) Failure of others to develop a PDE4 inhibitor

673. Many others failed to develop a PDE4 inhibitor. *See* PF ¶¶ 674–724.

674. Finding a successful PDE4 inhibitor, even in 2020, has been a challenge. Trial Tr. at 761:12–16 (Page Cross 6.18.21).

675. Apremilast succeeded where other PDE4 inhibitors failed. Trial Tr. at 220:18–20 (Knowles Direct 6.15.21).

676. By 1999, a hundred or more PDE4 inhibitor candidates had been discussed in the published literature. Trial Tr. at 221:3–13 (Knowles Direct 6.15.21).

677. By 1999, it was publicly known that more than fifteen PDE4 inhibitors had been in clinical studies. Trial Tr. at 213:17–214:19 (Knowles Direct 6.15.21) (discussing five compounds in Phase 1 clinical trials, three compounds in Phase 2 clinical trials, two compounds in Phase 3 clinical trials, six compounds which had entered clinical trials but were discontinued); JTX-137 at JTX-137_2, JTX-137_6, JTX-137_7; JTX-67 at JTX-67_3–5; JTX-142 at JTX-142_4–5.

678. The articles relied upon by Dr. Knowles, including Dyke 1999, Norman 1999, and Norman 2002 are "good reviews written by people with experience in the fields" and are "a good summary of what was going on." Trial Tr. at 748:17–749:9 (Page Cross 6.18.21).

679. Of the compounds discussed in Dyke 1999 and Burnouf 1998, all but roflumilast have been discontinued by now. Trial Tr. at 227:7–21 (Knowles Direct 6.15.21) (referencing PDX4-12); JTX-137 at JTX-137_2; JTX-67 at JTX-67_5.

PDE4 Inhibitor Compounds as of October 1999

Preclinical Evaluation	Phase 1 Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Discontinued
AWD-12-281 (asthma and allergic rhinitis)	CI-1018 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Rolipram (depression)
RS-17597	T-440 (asthma)	V-11294A (asthma)	Roflumilast (COPD and asthma)	Filaminast (asthma)
Org-20241 (asthma)	YM-58997 (asthma)	Atizoram (atopic dermatitis)		Piclamilast (asthma)
	D-22888 (asthma)			CDP-840 (asthma)
	Arofylline (asthma)			D-4418 (asthma)
				Ro-201724 (psoriasis)

JTX-137 at 2 (rolipram), 6 (T-440), 7 (RS-17597)
JTX-67 at 3–5 (T-440, AWD-12-281), 5–7 (Ro-201724, filaminast, piclamilast, CDP-840, atizoram, D-4418, cilomilast, CI-1018, D-22888, YM-58997, arofylline), 8 (AWD-12-281), 11 (atizoram), 12 (Ro-201724)
JTX-142 at 4–5 (cilomilast, roflumilast, CDC-801, V-11294A)
PTX-497 at 6 (Org-20241)

PDX4-12

680. Many PDE4 inhibitors were discontinued due to side effects or lack of efficacy at tolerable doses. Trial Tr. at 222:22–224:20 (Knowles Direct 6.15.21); JTX-137 at JTX-137_2; JTX-67 at JTX-67_7, JTX-67_11.

681. As even Dr. Page agreed, some drugs were stopped because they have a deficiency in efficacy and safety and sometimes both. Trial Tr. at 762:6–11 (Page Cross 6.18.21).

682. For a number of compounds, no reason for discontinuation is reported; however, it is quite common either not to report or to delay reporting on compounds that are not being progressed, if they have been discontinued. Trial Tr. at 227:1–6 (Knowles Direct 6.15.21).

(1) Compounds taken into clinic but discontinued

683. As of 1999 or 2002, many PDE4 inhibitors had been advanced into clinical studies, but were ultimately discontinued due to safety or efficacy reasons, thus confirming that many others had tried and failed to develop a PDE4 inhibitor. *See* PF ¶ 684–724.

684. As of 1999 or 2002 "there were a lot of companies who were developing PDE4 inhibitors." Trial Tr. at 747:3–6 (Page Cross 6.18.21).

685. A lot of the PDE4 inhibitors that were being developed as of 1999 or 2002 "failed or didn't progress." Trial Tr. at 747:13–18 (Page Cross 6.18.21).

686. As of 1999, rolipram, atizoram, CDP-840, filaminast, piclamilast and D-4418 had been taken into clinical studies, but they all failed. Trial Tr. at 222:22–225:14, (Knowles Direct 6.15.21) (referencing PDX4-15).

PDE4 Inhibitors Reported as Discontinued by October 1999

Company	Compound	Indication	Phase	Reason for Discontinuation
Schering	Rolipram	Depression	Phase 2	Unacceptable side effects
Pfizer	Atizoram	Asthma	Phase 2	Emesis and short plasma half-life
Celltech	CDP-840	Asthma	Phase 2	Lack of efficacy
Wyeth-Ayerst	Filaminast	Asthma	Phase 2	Not stated
Rhône-Poulenc	Piclamilast	Asthma	Phase 2	Side effects and poor pharmacokinetics
Chiroscience	D-4418	Asthma	Phase 2	Not stated

JTX-137 at 2 (rolipram)
JTX-67 at 5 (atizoram, CDP-840, filaminast, piclamilast, D-4418)

PDX4-15

687. As of 1999, rolipram, a Schering PDE4 inhibitor, was discontinued due to emesis. Trial Tr. at 222:22–223:18 (Knowles Direct 6.15.21); JTX-137 at JTX-137_2.

688. As of 1999, atizoram, a Pfizer PDE4 inhibitor, was discontinued because it was not effective at tolerable doses; and was never approved for atopic dermatitis. Trial Tr. at 223:19–224:13, 225:4–8 (Knowles Direct 6.15.21); JTX-67 at JTX-67_11, JTX-67_7.

689. As of 1999, CDP-840, a selective PDE4 inhibitor, "was discontinued in 1996 due to disappointing efficacy." Trial Tr. at 224:14–20 (Knowles Direct 6.15.21); JTX-67 at JTX-67_7.

690. As of 1999, filaminast, a selective PDE4 inhibitor, has apparently been terminated with no clinical data reported. Trial Tr. at 224:21–24 (Knowles Direct 6.15.21); JTX-67 at JTX-67_7.

691. As of 1999, piclamilast, a selective PDE4 inhibitor had been discontinued due to problems with side effects and poor pharmacokinetics. Trial Tr. at 224:25–225:3 (Knowles Direct 6.15.21); JTX-67 at JTX-67_7.

692. As of 1999, no reason was provided for why D-4418 had been discontinued, but by now it most certainly has been discontinued. Trial Tr. at 221:17–222:21, 225:9–14 (Knowles Direct 6.15.21).

693. As of 1999, at least six PDE4 inhibitors had been discontinued. Trial Tr. at 214:3–19, 221:25–225:14 (Knowles Direct 6.15.21).

694. As of March 2002, arofylline, CI-1018, tibenelast, D-22888, V-11294A, YM-976 and BAY-19-8004 had been taken into clinic, but they all failed. Trial Tr. at 225:15–226:25 (Knowles Direct 6.15.21) (referencing PDX4-16); PTX-497 at PTX-497_3–6; JTX-282 at JTX-282_1, JTX-282_4.

Additional PDE4 Inhibitors Reported as Discontinued by March 2002

Company	Compound	Indication	Phase	Reason for Discontinuation
Almirall Profesfarma	Arofylline	Asthma	Phase 3	Unacceptable side effects
Pfizer	CI-1018	Asthma	Phase 1	Teratogenicity
Eli Lilly	Tibenelast	Asthma	Phase 2	Not stated
Asta Medica	D-22888	Asthma	Not stated	Not stated
Napp	V-11294A	Asthma	Not stated	Not stated
Yamanouchi	YM-976	Asthma	Not stated	Not stated
Bayer	BAY-19-8004	Asthma	Not stated	Not stated

PTX-497 at 3 (arofylline), 4 (CI-1018), 5 (tibenelast), 6 (D-22888)
JTX-282 at 1 (V-11294A, YM-976), 4 (BAY-19-8004)

PDX4-16

695. As of March 2002, arofylline, a selective oral PDE4 inhibitor in development for asthma was discontinued due to undesirable side effects. Trial Tr. at 226:4–12 (Knowles Direct 6.15.21); PTX-497 at PTX-497_3.

696. As of March 2002, CI-1018, a selective PDE4 inhibitor was discontinued at Phase 1 because of teratogenicity. Trial Tr. at 226:13–18 (Knowles Direct 6.15.21); PTX-497 at PTX-497_4.

697. As of March 2002, tibenelast, D-22888, V-11294A, YM-976 and BAY-19-8004 had been discontinued. Trial Tr. at 226:19–227:6 (Knowles Direct 6.15.21); JTX-282 at JTX-282_1, JTX-282_4; PTX-497 at PTX-497_5–6.

698. As of March 2002, at least thirteen PDE4 inhibitors had been discontinued. *See* Trial Tr. at 215:18–216:4, 221:25–225:14 (Knowles Direct 6.15.21).

699. Holding a compound with good properties of efficacy, safety and drug-like properties is a valuable asset and it would be unusual to discontinue such a compound. Trial Tr. at 227:25–228:8 (Knowles Direct 6.15.21).

700. If a compound were a valuable asset, even if the company changed strategies, such that they did not want to develop the compound itself, they would "almost certainly" seek to out-license to somebody else to realize some of the value of that asset. Trial Tr. at 227:25–228:8 (Knowles Direct 6.15.21).

701. Dr. Knowles testified that in his more than 30 years of experience in drug discovery, he cannot remember encountering a situation where a company discontinued development of a compound for reasons unrelated to shortcomings in that compound's properties. Trial Tr. at 228:9–14 (Knowles Direct 6.15.21).

702. Dr. Page provided V11294A as an example of a compound discontinued for reasons other than its shortcomings as a PDE4 inhibitor, but provided no explanation as to why it was discontinued, and admitted that he does not even know if its developer tried to sell it, but was unsuccessful. Trial Tr. at 762:12–763:7, 763:24–764:1, 765:24–766:2 (Page Cross 6.18.21).

703. A 2008 reference by Dr. Giembycz, an expert in phosphodiesterase inhibitors, lists that V-11294A was discontinued for efficacy reasons. Trial Tr. at 766:3–768:14 (Page Cross 6.18.21); PTX-427 at PTX-427_1.

704. Dr. Page alluded to having referred to another compound in his expert report as one he understood had been discontinued for reasons unrelated to shortcomings in the compound. The compound Dr. Page noted in his expert report but did not testify about at trial was CDP-840. Contrary to Dr. Page's assertion, the literature reported that CDP840 was discontinued because of "disappointing efficacy." Trial Tr. at 224:14–20 (Knowles Direct 6.15.21); JTX-67 at JTX-67_7; *see also* PTX-427 at PTX-427_1.

705. Dr. Giembycz also reports that by 2008, "the development of PDE4 inhibitors of various structural classes, including cilomilast, filaminast, lirimilast, piclamilast, tofimilast, AWD-12-281 (*aka* GSK 842470), CDP840, CI-1018, D-4418, IC485, L-826,141, SCH 351391 and V11294A has been discontinued due to lack of efficacy." PTX-427 at PTX-427_1.

706. Even today, companies are still attempting—and failing—to develop PDE4 inhibitors. *See* Trial Tr. at 749:10–19 (Page Cross 6.18.21).

707. GSK, Gilead, and Pfizer have discontinued their PDE4 inhibitor projects. Trial Tr. at 760:3–8, 750:18–751:24 (Page Cross 6.18.21) (discussing Table 1: Discontinued inhaled PDE4 inhibitors from JTX-166 at JTX-166_4); JTX-166 at JTX-166_2–4.

TABLE 1 | Discontinued inhaled PDE4 inhibitors.

Name/ Company	Disease indications	Development stage (Last development reported)
AWD-12-281 Elbion/GSK	COPD Asthma	Phase II (2006) Phase II (2003)
Tofimilast Pfizer	COPD Asthma	Phase II (2007) Phase II (2007)
UK-500,001 Pfizer	COPD	Phase II (2009)
GSK256066 GlaxoSmith Kline	COPD Asthma	Phase II (2013) Phase II (2010)
12b AstraZeneca	COPD	Discovery (2014)
SCH900182 Schering Plough/Merck	Asthma	Discovery (2013)
GS-5759 Gilead	COPD	Discovery (2017)

708. AWD-12-281, an inhaled PDE4 inhibitor developed by Elbion/GSK, was discontinued due to poor efficacy in 2006. JTX-166 at JTX-166_2.

709. Tofimilast, a PDE4 inhibitor developed by Pfizer, "failed to demonstrate efficacy at any dose and development has been discontinued." JTX-166 at JTX-166_2; Trial Tr. at 750:18–24 (Page Cross 6.18.21).

710. UK-500,001, a moderately potent PDE4 inhibitor developed by Pfizer, "was discontinued in 2006 due to lack of efficacy in COPD patients and the results of the clinical study raised doubt about the potential of inhaled PDE4 inhibitors in COPD." JTX-166 at JTX-166_2 (citation omitted); Trial Tr. at 750:25–751:4 (Page Cross 6.18.21).

711. GSK256066, an inhaled PDE4 inhibitor developed by GSK, "was no longer listed on the GSK development pipeline in 2012," and "potentially hampering clinical development, a low therapeutic index for GSK256066 was revealed by a 14-day inhalation

toxicology study in rats." JTX-166 at JTX-166_2; Trial Tr. at 751:5–751:18 (Page Cross 6.18.21).

712. SCH900182, developed by Schering Plough and Merck, "is a highly potent PDE4 inhibitor," "yet the compound has not advanced past preclinical development." JTX-166 at JTX-166_2.

713. While AstraZeneca developed a highly potent PDE4 inhibitor called 12b, it "currently has no PDE4 inhibitors" in the pipeline. JTX-166 at JTX-166_3.

714. GS-5759, a moderately potent PDE4 inhibitor developed by Gilead, "is assumed to be discontinued as no development has been reported." JTX-166 at JTX-166_3.

715. Almirall reported two potent PDE4 inhibitor series, but these "compounds are not planned to advance past preclinical development." JTX-166 at JTX-166_4.

716. Dr. Page has been involved in developing 15–20 PDE4 inhibitors since 1984: except for roflumilast, none of them have been FDA-approved. Trial Tr. at 761:17–24 (Page Cross 6.18.21). Dr. Page also never worked on thalidomide analogs. Trial Tr. at 769:13–22 (Page Cross 6.18.21).

(2) No compounds in clinical studies in October 1999 or March 2002 other than roflumilast, are still in development or are FDA approved.

717. As of 1999 or 2002, many PDE4 inhibitors had been published as being in pre-clinical studies, but were ultimately discontinued due to safety or efficacy reasons, thus further confirming that many others had tried and failed to develop a PDE4 inhibitor. *See* PF ¶ 699–701, 719–20.

718. As of October 1999, CI-1018, T-440, YM-58997, D-22888, arofylline, CDC-801, V-11294A, atizoram, cilomilast, and roflumilast were still in some phase of clinical studies. Trial Tr. at 212:3–18, 227:7–11 (Knowles Direct 6.15.21) (referencing PDX4-12);

JTX-137 at JTX-137_2, JTX-137_6; JTX-67 at JTX-67_3–7, JTX-67_11–12; JTX-142 at JTX-142_4–5.

PDE4 Inhibitor Compounds as of October 1999

Preclinical Evaluation	Phase 1 Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Discontinued
AWD-12-281 (asthma and allergic rhinitis)	CI-1018 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Rolipram (depression)
RS-17597	T-440 (asthma)	V-11294A (asthma)	Roflumilast (COPD and asthma)	Filaminast (asthma)
Org-20241 (asthma)	YM-58997 (asthma)	Atizoram (atopic dermatitis)		Piclamilast (asthma)
	D-22888 (asthma)			CDP-840 (asthma)
	Arofylline (asthma)			D-4418 (asthma)
				Ro-201724 (psoriasis)

JTX-137 at 2 (rolipram), 6 (T-440), 7 (RS-17597)
JTX-67 at 3–5 (T-440, AWD-12-281), 5–7 (Ro-201724, filaminast, piclamilast, CDP-840, atizoram, D-4418, cilomilast, CI-1018, D-22888, YM-58997, arofylline), 8 (AWD-12-281), 11 (atizoram), 12 (Ro-201724)
JTX-142 at 4–5 (cilomilast, roflumilast, CDC-801, V-11294A)
PTX-497 at 6 (Org-20241)

PDX4-12

719. Other than roflumilast, of the compounds cited in the literature in October 1999, including AWD-12-281, RS-17597, Org-20241, CI-1018, T-440, YM-58997, D-22888, arofylline, CDC-801, V-11294A, atizoram, cilomilast, roflumilast, rolipram, filaminast, piclamilast, CDP-840, D-4418 and Ro-201724, none have been approved for use as of today. Trial Tr. at 227:12–16 (Knowles Direct 6.15.21) (referencing PDX4-12); JTX-137 at JTX-137_2, JTX-137_6, JTX-137_7; JTX-67 at JTX-67_3–8, JTX-67_11-12; JTX-142 at JTX-142_4–5; PTX-497 at PTX-497_6.

PDE4 Inhibitor Compounds as of October 1999

Preclinical Evaluation	Phase 1 Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Discontinued
AWD-12-281 (asthma and allergic rhinitis)	CI-1018 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Rolipram (depression)
RS-17597	T-440 (asthma)	V-11294A (asthma)	Roflumilast (COPD and asthma)	Filaminast (asthma)
Org-20241 (asthma)	YM-58997 (asthma)	Atizoram (atopic dermatitis)		Piclamilast (asthma)
	D-22888 (asthma)			CDP-840 (asthma)
	Arofylline (asthma)			D-4418 (asthma)
				Ro-201724 (psoriasis)

JTX-137 at 2 (rolipram), 6 (T-440), 7 (RS-17597)
JTX-67 at 3–5 (T-440, AWD-12-281), 5–7 (Ro-201724, filaminast, piclamilast, CDP-840, atizoram, D-4418, cilomilast, CI-1018, D-22888, YM-58997, arofylline), 8 (AWD-12-281), 11 (atizoram), 12 (Ro-201724)
JTX-142 at 4–5 (cilomilast, roflumilast, CDC-801, V-11294A)
PTX-497 at 6 (Org-20241)

PDX4-12

720. If a PDE4 inhibitor had been under development in 1999, but has not yet been approved as of today, it has almost certainly been discontinued. Trial Tr. at 227:17–21 (Knowles Direct 6.15.21).

721. As of March 2002, CDC-801, BAY-19-8004, pumafentrine, cipamfylline, mesopram, cilomilast and roflumilast were still in some phase of clinical studies. Trial Tr. at 214:20–215:17, 227:7–24 (Knowles Direct 6.15.21) (referencing PDX4-13); JTX-282 at JTX-282_1, JTX-282_2, JTX-282_4.

PDE4 Inhibitor Compounds as of March 2002

Phase I Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Additional Discontinued
SCH-351591 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Arofylline (asthma)
CI-1044 (COPD and asthma)	BAY-19-8004 (COPD and asthma)	Roflumilast (COPD and asthma)	Atizoram (asthma)
	Pumafentrine (asthma)		Tibenelast
	Cipamfylline (dermatitis)		CI-1018 (asthma)
	Mesopram (multiple sclerosis)		D-22888 (asthma)
			V-11294A (asthma)
			YM-976 (asthma)

PTX-497 at 3 (arofylline), 4 (CI-1018), 5 (atizoram, tibenelast), 6 (D-22888)
JTX-282 at 1 (V-11294A, YM-976), 2 (SCH-351591, CI-1044, cilomilast, roflumilast, BAY-19,8004, pumafentrine, CDC-801, cipamfylline, mesopram), 4 (BAY-19-8004)

PDX4-13

722. Other than roflumilast, of the compounds cited in the literature in March 2002, including SCH-351591, CI-1044, CDC-801, BAY-19-8004, pumafentrine, cipamfylline, mesopram, cilomilast, roflumilast, arofylline, atizoram, tibenelast, CI-1018, D-22888, V-11294A, and YM-976, none have been approved for use as of today. Trial Tr. at 227:12–24 (Knowles Direct 6.15.21) (referencing PDX4-13); JTX-282 at JTX-282_1, JTX-282_2, JTX-282_4; PTX-497 at PTX-497_3–6.

PDE4 Inhibitor Compounds as of March 2002

Phase I Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Additional Discontinued
SCH-351591 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Arofylline (asthma)
CI-1044 (COPD and asthma)	BAY-19-8004 (COPD and asthma)	Roflumilast (COPD and asthma)	Atizoram (asthma)
	Pumafentrine (asthma)		Tibenelast
	Cipamfylline (dermatitis)		CI-1018 (asthma)
	Mesopram (multiple sclerosis)		D-22888 (asthma)
			V-11294A (asthma)
			YM-976 (asthma)

PTX-497 at 3 (arofylline), 4 (CI-1018), 5 (atizoram, tibenelast), 6 (D-22888)
JTX-282 at 1 (V-11294A, YM-976), 2 (SCH-351591, CI-1044, cilomilast, roflumilast, BAY-19,8004, pumafentrine, CDC-801, cipamfylline, mesopram), 4 (BAY-19-8004)

PDX4-13

723. If a PDE4 inhibitor had been under development in 2002, but has not yet been approved as of today, it has almost certainly been discontinued. Trial Tr. at 227:17–24 (Knowles Direct 6.15.21).

724. As of today, at least 37 PDE4 inhibitors had been discontinued. *See* JTX-166; JTX-427; Trial Tr. at 227:12–24; PTX-497; JTX-282; JTX-137; JTX-67; JTX-142.

(3) A nexus exists between the asserted claims of the ’638 and ’536 Patents and the failure of others.

725. The asserted claims of the ’638 Patent claim a pharmaceutical composition comprising stereomerically pure apremilast. JSF ¶¶ 26–31 (ECF No. 422).

726. The asserted claims of the ’536 Patent claim a method of treating psoriasis, which comprises orally administering to a patient having psoriasis, stereomerically pure apremilast. JSF ¶¶ 40–41 (ECF No. 422).

727. The problem that others in the industry sought to solve was finding a PDE4 inhibitor that had sufficient anti-inflammatory activity but that did not have the side effects and tolerability issues that plagued the PDE4 inhibitors in the prior art. Trial Tr. 219:13–220:1 (Knowles Direct 6.15.21).

728. The asserted claims of the ’638 and ’536 Patents are directed to stereomerically pure apremilast, a selective PDE4 inhibitor with suitable potency, safety, drug-like properties, and a sufficiently high therapeutic index to make it suitable for a pharmaceutical composition to treat humans, that fills a substantial need in patients who have psoriasis and other inflammatory diseases. Trial Tr. 219:8–220:15 (Knowles Direct 6.15.21).

b) Long-felt need for a PDE4 inhibitor

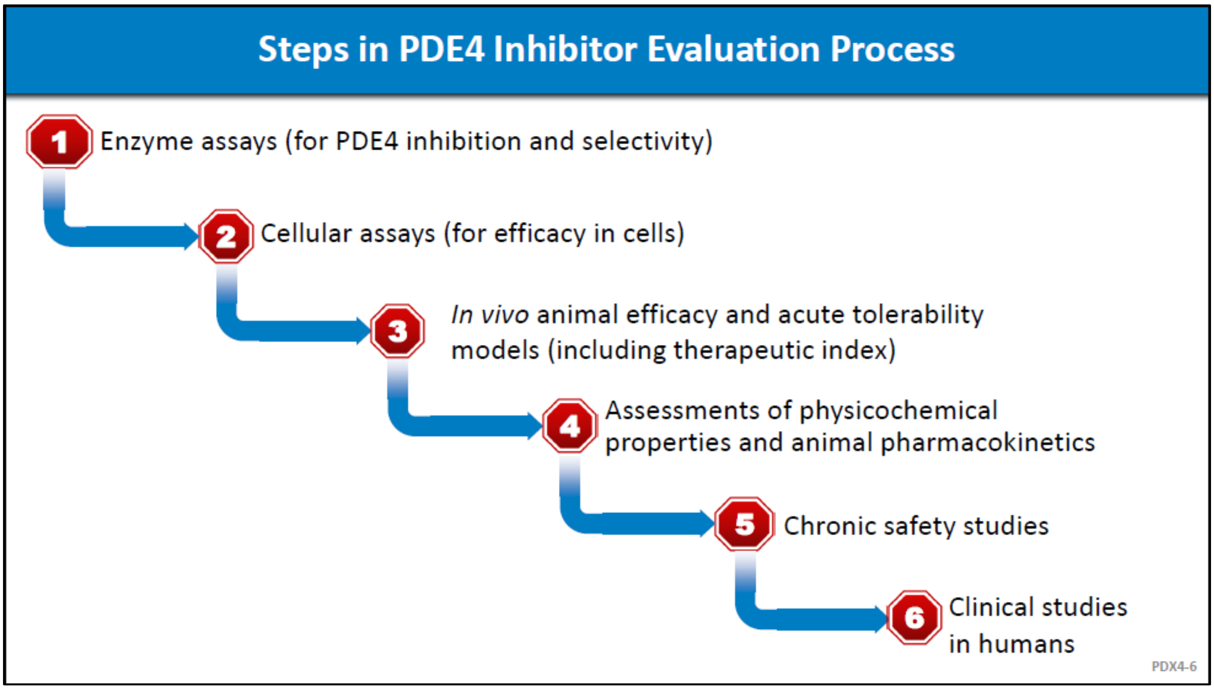
729. Otezla met a long-felt need for a PDE4 inhibitor suitable for use as a pharmaceutical composition that was effective and minimized side effects. Trial Tr. at 217:20–218:1 (Knowles Direct 6.15.21).

730. By October 1999 and by March 2002, many, if not most, pharmaceutical companies were interested in PDE4 inhibitors because they believed a PDE4 inhibitor with the right properties would fulfill a long-felt need for new treatments for inflammation, and could be safer and more tolerable than existing treatments including steroids. Trial Tr. at 218:2–14, 218:23–219:7 (Knowles Direct 6.15.21); 141:15–18 (Schafer Direct 6.14.21); JTX-137 at JTX-137_1.

731. By October 1999, there were hundreds of compounds reported in the literature as potentially exhibiting PDE4 inhibitory activity. Trial Tr. at 221:3–8 (Knowles Direct 6.15.21); *see also* JTX-142 at JTX-142_2–5.

732. The vast majority of compounds that showed PDE4 inhibitory activity in the initial enzyme study would ultimately fail to reach clinical studies in humans. Trial Tr. at 209:23–210:3 (Knowles Direct 6.15.21).

733. In October 1999, only very rarely would PDE4 inhibitor candidates pass through the stages of drug development and make it into clinical trials. Trial Tr. at 210:4–7 (Knowles Direct 6.15.21) (referencing PDX4-6).



734. By 1999, PDE4 inhibitors as a class were well-understood to be associated with a number of common side effects, particularly nausea and emesis. Trial Tr. at 250:21–261:1 (Knowles Cross 6.15.21); 268:6–13 (Knowles Redirect 6.15.21); JTX-67 at JTX-67_7. ("The development of drugs of this class has been hampered by adverse events, particularly nausea and emesis."); JTX-137 at JTX-137_15.

735. In 1998, scientists in the field looking for PDE4 inhibitors observed that "the obvious therapeutic goal [was] to optimize on the anti-inflammatory actions of PDE4 inhibitors while formulating strategies to limit their side effects." JTX-137 at JTX-137_1.

736. Said differently, in 1998, "the obvious therapeutic goal" was to find compounds which had anti-inflammatory actions of PDE4 inhibitors without having side effects and tolerability issues that plagued many of the PDE4 inhibitors at that time. Trial Tr. at 219:13–220:1 (Knowles Direct 6.15.21); JTX-137 at JTX-137_1.

737. Even as late as 2020, journal articles reported that "[t]he primary problem with oral PDE4 inhibitors is the low therapeutic index of these compounds, which severely limits the dose that can be given." JTX-166 at JTX-166_2; Trial Tr. at 753:2–7 (Page Cross 6.18.21).

738. Given the tolerability problems encountered with PDE4 inhibitors, researchers considered other delivery routes, such as topical administration and inhalation, with the hope that they would avoid side effects. Trial Tr. at 1695:20–25 (Knowles Direct 6.25.21).

739. Local or topical administration is intended to have an effect at the site where the drug is placed. In contrast, systemic delivery, most often through oral administration, exposes the whole body to the drug, which has the advantage of having effect on multiple sites of the body, but may have the disadvantage of causing safety or tolerability issues. Trial Tr. at 1697:17–1698:1 (Knowles Direct 6.25.21).

740. It was hoped and anticipated that inhalation would have less tolerability and safety issues than oral administration. Trial Tr. at 1696:1–5 (Knowles Direct 6.25.21); JTX-

166 at JTX-166_2 ("Inhaled administration represents another potential approach to improve the therapeutic index of PDE4 inhibitors."); JTX-67 at JTX-67_7 ("A final strategy, which may allow separation of efficacy from side effects, is to dose directly into the lung thus minimisting [sic] systemic exposure to inhibitors." (citation omitted)).

741. By October 1999, and by March 2002, the need for a PDE4 inhibitor suitable for use as a pharmaceutical composition to treat humans had not been filled. Trial Tr. at 218:2–22 (Knowles Direct 6.15.21); JTX-137 at JTX-137_15 ("It has yet to be determined whether the second generation of PDE4 inhibitors will overcome emesis and other GI side effects to allow the full therapeutic potential of these compounds to be realized."); JTX-67 at JTX-67_7.

742. None of the hundreds of PDE4 inhibitors in development had received FDA approval by October 1999 or March 2002. Trial Tr. at 221:3–8, 221:14–16 (Knowles Direct 6.15.21); *see also* JTX-142 at JTX-142_3–5.

743. Of the PDE4 compounds in development in October 1999 or March 2002, only roflumilast has been approved by the FDA, which happened in 2011. Trial Tr. at 216:10–217:4 (Knowles Direct 6.15.21) (referencing PDX4-12 and PDX4-13); JTX-166 at JTX-166_1.

PDE4 Inhibitor Compounds as of October 1999

Preclinical Evaluation	Phase 1 Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Discontinued
AWD-12-281 (asthma and allergic rhinitis)	CI-1018 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Rolipram (depression)
RS-17597	T-440 (asthma)	V-11294A (asthma)	Roflumilast (COPD and asthma)	Filaminast (asthma)
Org-20241 (asthma)	YM-58997 (asthma)	Atizoram (atopic dermatitis)		Piclamilast (asthma)
	D-22888 (asthma)			CDP-840 (asthma)
	Arofylline (asthma)			D-4418 (asthma)
				Ro-201724 (psoriasis)

JTX-137 at 2 (rolipram), 6 (T-440), 7 (RS-17597)
JTX-67 at 3–5 (T-440, AWD-12-281), 5–7 (Ro-201724, filaminast, piclamilast, CDP-840, atizoram, D-4418, cilomilast, CI-1018, D-22888, YM-58997, arofylline), 8 (AWD-12-281), 11 (atizoram), 12 (Ro-201724)
JTX-142 at 4–5 (cilomilast, roflumilast, CDC-801, V-11294A)
PTX-497 at 6 (Org-20241)

PDX4-12

PDE4 Inhibitor Compounds as of March 2002

Phase I Clinical Study	Phase 2 Clinical Study	Phase 3 Clinical Study	Additional Discontinued
SCH-351591 (asthma)	CDC-801 (Crohn's Disease)	Cilomilast/Ariflo (COPD and asthma)	Arofylline (asthma)
CI-1044 (COPD and asthma)	BAY-19-8004 (COPD and asthma)	Roflumilast (COPD and asthma)	Atizoram (asthma)
	Pumafentrine (asthma)		Tibenelast
	Cipamfylline (dermatitis)		CI-1018 (asthma)
	Mesopram (multiple sclerosis)		D-22888 (asthma)
			V-11294A (asthma)
			YM-976 (asthma)

PTX-497 at 3 (arofylline), 4 (CI-1018), 5 (atizoram, tibenelast), 6 (D-22888)
JTX-282 at 1 (V-11294A, YM-976), 2 (SCH-351591, CI-1044, cilomilast, roflumilast, BAY-19,8004, pumafentrine, CDC-801, cipamfylline, mesopram), 4 (BAY-19-8004)

PDX4-13

744. Apremilast, in the form of Otezla, is the only FDA approved PDE4 inhibitor for the treatment of psoriasis. Trial Tr. at 217:8–11 (Knowles Direct 6.15.21).

745. When apremilast was approved and used in patients, it became known to the public, to doctors and patients and the medical community, that apremilast had achieved the therapeutic goal of finding compounds which had anti-inflammatory actions of PDE4 inhibitors without having the side-effect and tolerability issues that plagued many of the PDE4 inhibitors at that time. Trial Tr. at 219:13–220:9 (Knowles Direct 6.15.21).

746. Apremilast met the long-felt need for a PDE4 inhibitor suitable for use as a pharmaceutical composition that was effective and minimized side effects, and as a consequence has filled a substantial need in patients who have psoriasis, psoriatic arthritis, and Behcet's disease. Trial Tr. at 217:20–218:1, 219:13–220:15 (Knowles Direct 6.15.21).

(1) Roflumilast did not satisfy the long-felt need.

747. Roflumilast did not fully meet a long-felt need for a PDE4 inhibitor. PF ¶¶ 748–50.

748. Roflumilast was approved by FDA in 2011. Trial Tr. at 754:8–12 (Page Cross 6.18.21); JTX-166 at JTX-166_1.

749. Roflumilast, the only other PDE4 inhibitor to be approved for clinical use (in 2011), is only approved only for a relatively narrow subgroup of patients with chronic obstructive pulmonary disease, who have severe disease, have chronic bronchitis, and who are subject to frequent exacerbations. Trial Tr. at 216:5–21, 227:12–16 (Knowles Direct 6.15.21).

750. And roflumilast is not particularly well tolerated, as "the maximum tolerated dose of roflumilast is near the bottom of the efficacy dose-response curve." JTX-166 at JTX-166_2; Trial Tr. at 753:23–754:12 (Page Cross 6.18.21); *see also* JTX-166 at JTX-166_2 ("Roflumilast was approved by the FDA in 2011 despite its relatively poor tolerability."); JTX-231 at JTX-231_2 ("[T]he selective PDE4 inhibitor roflumilast is licensed as an oral treatment for distinct subsets of patients with severe COPD . . . , but poor tolerability limits the usefulness of this drug."); Trial Tr. at 755:16–756:2, 758:5–758:25 (Page Cross 6.18.21) ("In marked contrast, an independent NIH-funded study utilizing data on trials with roflumilast released by the FDA concluded that . . . 'Our systematic and transparent benefit harm assessment of roflumilast for COPD patients with a history of exacerbations suggests that roflumilast has no benefit for most patients.'").

(2) A nexus exists between the asserted claims of the '638 and '536 Patents and the long-felt need for a PDE4 inhibitor.

751. The asserted claims of the '638 Patent claim a pharmaceutical composition comprising stereomerically pure apremilast. JSF ¶¶ 26–31 (ECF No. 422).

752. The asserted claims of the '536 Patent claim a method of treating psoriasis, which comprises orally administering to a patient having psoriasis, stereomerically pure apremilast. JSF ¶¶ 40–41 (ECF No. 422).

753. The asserted claims of the '638 and '536 Patents allowed apremilast to succeed where other PDE4 inhibitors failed, and deliver a selective PDE4 inhibitor with suitable potency, safety, drug-like properties, and a sufficiently high therapeutic index to make it

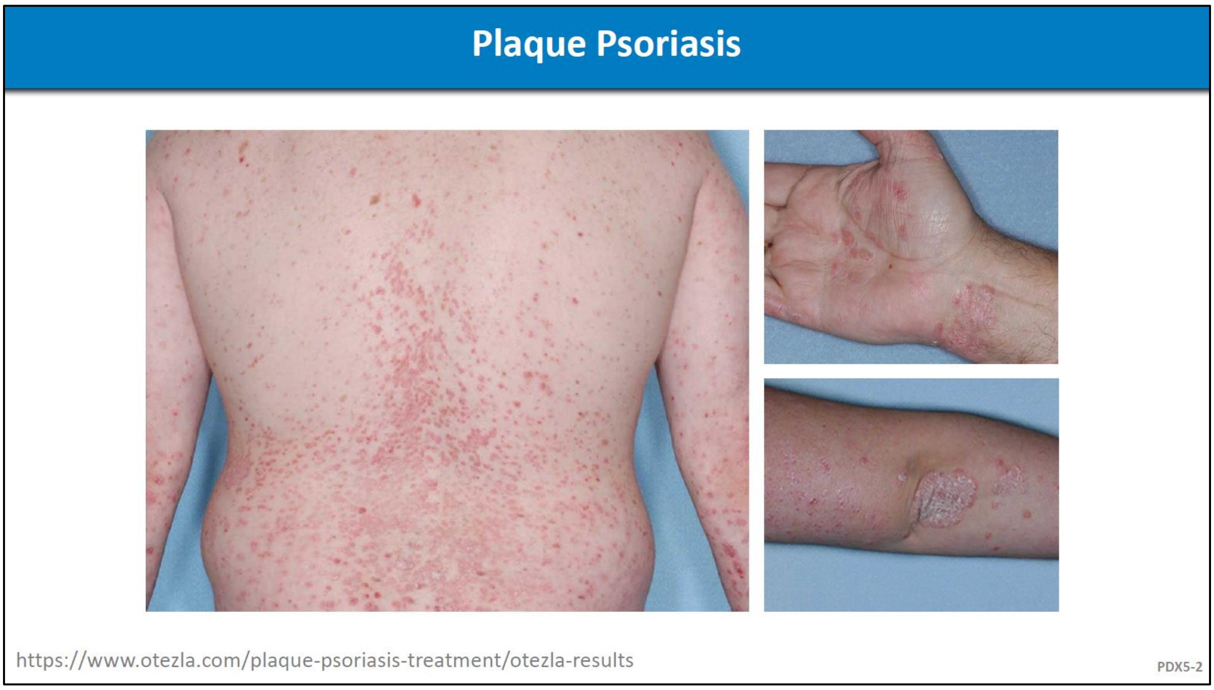
suitable for a pharmaceutical composition to treat humans, and to fill a substantial need in patients who have psoriasis and other inflammatory diseases. Trial Tr. 219:8–220:15 (Knowles Direct 6.15.21).

c) Long-felt need for a psoriasis treatment

(1) Otezla and psoriasis background

754. In October 1999 and until Otezla became available, there was a long-felt and unmet need for a treatment for plaque psoriasis, particularly moderate plaque psoriasis, that was safer than prior art treatments, that was effective, and that lacked common barriers to adherence. Trial Tr. at 286:1–22 (Alexis Direct 6.15.21).

755. Plaque psoriasis affects approximately 3 percent of the U.S. population, affects patients of nearly any age, and the patient population is roughly 50/50 males to females. Trial Tr. at 277:18–21, 296:15-17 (Alexis 6.15.21); 1756:20–25 (Alexis 6.25.21). It is currently an incurable chronic inflammatory or immune-mediated disorder of the skin, characterized by red, raised, scaly patches on the body called plaques that form on top of affected areas of the skin. Trial Tr. at 276:12–23, 278:22-25 (Alexis Direct 6.15.21); PDX5-2.



756. Plaques can spontaneously shed the scale causing patients to complain about flakes on their clothing or other surfaces. Trial Tr. at 276:12–277:1 (Alexis Direct 6.15.21).

757. Plaque psoriasis can cause intense itching and discomfort, where the plaques will often bleed when scratched and can be disfiguring and physically debilitating at times, especially impacting mobility and ability to perform common tasks at home and work if psoriasis affects a patient's hands or feet. Trial Tr. at 276:10–277:14 (Alexis Direct 6.15.21).

758. Psoriasis can also affect a patients' joints, resulting in stiffness, pain, and reduced mobility in the form of psoriasis called psoriatic arthritis, which affects about a third of psoriasis patients. Trial Tr. at 276:10–277:14 (Alexis Direct 6.15.21).

759. The red, scaly plaques and flaking caused by plaque psoriasis can have very negative physical and psychological impacts on patients' lives—patients describe feeling very self-conscious about any sort of public interaction, changing their choices in clothing, and limiting the activities they engage in. Trial Tr. at 284:23–285:15 (Alexis Direct 6.15.21).

760. The visibility of psoriasis plaques on the skin makes it impossible for patients to keep their disease private, and may subject patients to unwanted questions and unfair judgements by others. Trial Tr. at 284:23–285:24 (Alexis Direct 6.15.21).

761. Otezla is an oral medication approved in 2014 to treat adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Trial Tr. at 278:7–12, 279:3–6 (Alexis Direct 6.15.21); JTX-110 at JTX-110_1.

762. Otezla is also approved for adult patients with active psoriatic arthritis and adult patients with oral ulcers associated with Behcet's disease, both of which are currently incurable chronic diseases. Trial Tr. at 278:7–16, 278:22-25. (Alexis Direct 6.15.21); JTX-110 at JTX-110_1.

763. The active ingredient of Otezla is apremilast. Trial Tr. at 278:20–21 (Alexis Direct 6.15.21); JTX-110 at JTX-110_8.

764. Otezla works through a PDE4 inhibiting mechanism of action, which creates an anti-inflammatory effect but does not suppress the immune system (i.e., it is not an immunosuppressant). Trial Tr. at 278:7–19, 304:13–23. (Alexis Direct 6.15.21); JTX-110 at JTX-110_8.

(2) Other treatments failed to meet the need.

765. The primary psoriasis treatments available before Otezla received FDA approval in 2014 were topical treatments, older oral systemics, and biologics. Trial Tr. at 287:8–288:5 (Alexis Direct 6.15.21); PDX5-6.

Drawbacks of Approved Psoriasis Treatment Classes As of 2014

Class	Examples	Drawbacks		
		Safety	Efficacy	Barriers
Topicals	• Corticosteroids • Vitamin-D Analogues • Retinoids	• Skin atrophy • Skin fragility • Striae • Suppression of hypothalamic-pituitary-adrenal axis	• Insufficient for moderate-to-severe • Tachyphylaxis (loss of efficacy) • Does not treat concomitant psoriatic arthritis	• Makes tasks difficult when applied to hands • Difficulty of application • Stains clothes
Older oral systemics	• Methotrexate • Acitretin • Cyclosporine	• Concomitant disorders (*e.g.*, HIV) • Serious Infections • Fetal death and birth defects • Kidney and liver toxicity • Lymphoma • High blood pressure	• Acitretin has limited efficacy • Neither Acitretin nor Cyclosporine treats concomitant psoriatic arthritis	• Drug-drug interactions • Requires lab monitoring • Invasive liver biopsies
Biologics (post-2002)	• Remicade • Humira • Enbrel • Stelara	• Serious infections; risk of reactivation of TB • Malignancies		• Injectable or intravenous • Lab screening and monitoring • Cold storage requirements

PDX5-6

(a) Topicals

766. Topicals did not meet the need for a plaque psoriasis treatment that was safer, effective, and that lacked common barriers to adherence because the topical treatments available in the prior art had safety risks, were ineffective, and were burdensome in terms of application and damage to clothing and furniture as well as negative effects on day-to-day tasks and social interactions once applied. Trial Tr. at 287:12–25 (Alexis Direct 6.15.21); PTX-413 at PTX-413_1–2.

767. The topical treatments available in the prior art were not suitable for widespread psoriasis, because it was impractical for patients to apply the treatments to the entirety of the affected skin. Trial Tr. at 288:14–17, 289:5–9 (Alexis Direct 6.15.21).

768. The topical treatments available in the prior art were not effective for patients with moderate to severe psoriasis, and topical corticosteroids would lose their efficacy altogether over time, a phenomenon known as tachyphylaxis. Trial Tr. at 288:22–289:4 (Alexis Direct 6.15.21).

769. The topical treatments available in the prior art had no efficacy in addressing psoriatic arthritis, which affects about a third of patients with psoriasis. Trial Tr. at 288:18–21 (Alexis Direct 6.15.21).

770. The topical treatments available in the prior art carried barriers to adherence, including difficulty applying the treatments to the skin, and transferring to clothing or other surfaces once applied. Trial Tr. at 288:14–289:11 (Alexis Direct 6.15.21).

(b) Older oral systemics

771. The older oral systemics did not meet the need for a plaque psoriasis treatment that was safer, effective, and that lacked common barriers to adherence because of the serious safety risks oral treatments carried, as well as barriers often associated with their use such as the need for ongoing tests and lab monitoring and negative impacts on lifestyle including prohibitions on the consumption of alcohol. Trial Tr. at 281:21–284:4, 287:8–25, 289:12–291:12 (Alexis Direct 6.15.21); PTX-413.

772. Three oral systemic treatments were used prior to Otezla's approval, methotrexate, acitretin, and cyclosporine. Trial Tr. at 287:8–14, 289:12–14 (Alexis Direct 6.15.21).

773. Traditional systemic treatments including methotrexate and cyclosporine are associated with serious organ toxicity and severe adverse effects including liver damage and

require clinical monitoring throughout treatment. Trial Tr. 287:8–14, 289:12–291:12 (Alexis Direct 6.15.21); 938:5–939:12, 939:24–940:14 (Gilmore Cross 6.21.21); PTX-413 at PTX-413_1–2.

774. Methotrexate, acitretin and cyclosporine, each require monitoring before and during the course of treatment. Trial Tr. at 287:8–14, 289:15–21 (Alexis Direct 6.15.21).

775. Methotrexate was the most commonly used oral systemic psoriasis treatment prior to Otezla's approval. Trial Tr. at 287:8–14, 289:15–21, 292:14–18 (Alexis Direct 6.15.21).

776. In the relevant time period, guidelines for methotrexate called for invasive liver biopsies after a patient had taken a certain cumulative dose of the drug. Trial Tr. at 287:8–14, 291:2–5, 294:1–6 (Alexis Direct 6.15.21).

777. Methotrexate's label indicates it is only to be used in psoriasis patients with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy. Trial Tr. at 293:6–15 (Alexis Direct); PTX-413 at PTX-413_1, PTX-413_7.

WARNINGS

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY.

BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See **PRECAUTIONS.**)

PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS.**)
2. Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.
3. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). (See **PRECAUTIONS, Drug Interactions.**)
4. Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually

recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See **PRECAUTIONS, Organ System Toxicity,** *Hepatic*.)

5. Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
6. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
7. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
8. Like other cytotoxic drugs, methotrexate may induce Atumor lysis syndrome@in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
9. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy. (See **PRECAUTIONS, Organ System Toxicity,** *Skin*.)
10. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
11. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

778. Methotrexate is associated with fetal death and congenital anomalies, unexpectedly severe, sometimes fatal, bone marrow suppression, liver damage, potentially dangerous lung disease, and malignant lymphomas. Trial Tr. at 293:6–294:12 (Alexis Direct 6.15.21); PTX-413 at PTX-413_1.

779. Methotrexate is contraindicated for pregnant women, and is rarely appropriate for women of childbearing potential. Trial Tr. at 295:23–296:12 (Alexis Direct 6.15.21); PTX-413 at PTX-413_1–2.

780. Women of childbearing potential make up a very substantial segment of the psoriasis patient population. Trial Tr. at 296:13–296:21 (Alexis Direct 6.15.21).

781. Methotrexate was commonly used before Otezla's approval because it was one of few oral options available, and because there are some patients with severe psoriasis for

whom the overall potential benefits might outweigh the overall risks. Trial Tr. at 294:13–295:4 (Alexis Direct 6.15.21).

782. Patients taking methotrexate and acitretin must abstain from drinking alcohol, which can be difficult for many patients. Trial Tr. at 302:14–18 (Alexis Direct); *see also* Trial Tr. 938:9–17 (Gilmore Cross 6.21.21).

783. Use of cyclosporine is generally limited to one year for safety reasons, and the risk of permanent kidney damage increased considerably with longer use. Trial Tr. at 287:8–14, 291:2–12 (Alexis Direct 6.15.21).

784. It is a very common occurrence for patients to refuse to take methotrexate after hearing the warnings for the drug. Trial Tr. at 295:5–22 (Alexis Direct 6.15.21) ("For patients where I am advising them that they would have, as an option, this oral medication, methotrexate, when presenting them with the potential risks and safety considerations, blood test requirements, et cetera, it's extremely common -- in fact, almost the norm, at least, in my experience -- for patients to -- to have reservations about going on this medicine. Some of them will just reject it flat out, or those that really want to carefully consider it, they might take the information home, discuss with their family, come back for another follow-up visit to discuss some more, and often we'd end up with, no, Doc, I'm just not comfortable with this medication.").

785. Acitretin and methotrexate are associated with fetal death and birth defects. Trial Tr. at 287:8–14, 290:1–3 (Alexis Direct 6.15.21).

786. Acitretin has limited efficacy relative to other oral systemic treatments for psoriasis. Trial Tr. at 287:8–14, 209:12–20 (Alexis Direct 6.15.21).

787. Neither acitretin nor cyclosporine treat concomitant psoriatic arthritis. Trial Tr. at 287:8–14, 290:12–20 (Alexis Direct 6.15.21).

(c) Biologics

788. Biologic treatments failed to meet the need. Trial Tr. 299:18–22 (Alexis Direct 6.15.21).

789. Biologic treatments first began to receive FDA approval for the treatment of psoriasis after 2002. Trial Tr. at 287:24–25, 291:13–14 (Alexis Direct 6.15.21); 888:8–18 (Gilmore Direct 6.21.21). However, as of 2013, because long-term treatment of psoriasis with biologic therapies was often compromised by adverse events, there remained a need for an improved, orally available therapy for the treatment of psoriasis that limits disease progression without impacting patient lifestyle and wellbeing. Trial Tr. at 941:19–943:15 (Gilmore Cross 6.21.21).

790. Others in the medical community felt that even after the introduction of biologics for the treatment of psoriasis there remained an unmet need for a safer treatment, that was effective, and that lacked common barriers to adherence. Trial Tr. at 299:18–300:1 (Alexis Direct 6.15.21).

791. Biologic treatments were administered by subcutaneous injection, except for Remicade, which was administered via intravenous infusion at an infusion center. Trial Tr. at 287:8–14, 291:13–19 (Alexis Direct 6.15.21).

792. Dr. Gilmore's testimony that biologics' injectable route of administration is not often a barrier to patients was based on her experience with modern auto-injections. Trial Tr. 884:15–885:12 (Gilmore Direct 6.21.21)

793. When biologic treatments first became available for the treatment of psoriasis, they were distributed in pre-filled syringes requiring the patient to manually insert the needle of the syringe through their skin into the fatty layer before depressing the plunger to inject the medication. Trial Tr. at 324:20–25 (Alexis Cross 6.15.21).

794. Biologic treatments for psoriasis carry risks of serious infection, risk of reactivation of tuberculosis, and malignancies including lymphoma. Trial Tr. at 287:8–14, 291:20–22 (Alexis Direct 6.15.21).

795. Patients taking biologic treatments for psoriasis were required to submit to pre-testing before initiating treatment, and periodic testing during the course of treatment, which is a deterrent to many patients. Trial Tr. at 287:8–14, 291:22–292:7 (Alexis Direct 6.15.21).

796. The injectable or intravenous route of administration for biologics is a barrier to many patients, and before Otezla became available many patients were uncomfortable using the treatments. Trial Tr. at 281:21–284:9, 287:8–14, 292:3–6, 300:2–21, 302:24–303:13 (Alexis Direct 6.15.21); 1044:25–1045:11, 1045:25–1046:11 (Hofmann Cross 6.22.21). Counseling and patient education can overcome some patients' initial resistance to injectable therapies, but that at least 10 percent of Dr. Alexis's moderate-to-severe plaque psoriasis patients cannot be convinced to go on injectable therapies. Trial Tr. at 300:2–21, 302:24–303:13 (Alexis Direct 6.15.21). Biologics must be stored in refrigerated conditions, which can pose a barrier for many patients who may need to travel. Trial Tr. at 287:8–14, 292:8–12 (Alexis Direct 6.15.21).

(3) Otezla met the need.

797. Prior to Otezla's approval, there existed a long-felt and unmet need for a treatment for plaque psoriasis, particularly moderate plaque psoriasis, that was safer than prior art treatments, that was effective, and that lacked common barriers to adherence because of the drawbacks in the prior art treatments, as a result very sizable proportion of patients caught between ineffective topicals and oral and biologic treatments that carried significant safety risks and barriers to adherence, were undertreated and continued to suffer from the physical and psychological effects of the disease. Trial Tr. at 281:21–284:21 (Alexis Direct 6.15.21).

798. As of 2002, there remained a need for a safer, more effective and more convenient drug for treating patients suffering from psoriasis. Trial Tr. at 933:23–934:18, 941:6–18 (Gilmore Cross 6.21.21). In fact, Dr. Gilmore testified that in 2012, apremilast was recognized as possibly helping to fill a gap in the treatment of psoriasis because apremilast is dosed orally, offers an efficacious treatment option with an acceptable safety profile (e.g., no need for monitoring of liver and kidney function) and acceptable tolerability profile, as well as improved convenience compared to the available therapeutic options. Trial Tr. at 944:7–18 (Gilmore Cross 6.21.21). And biologics did not meet the need because as of 2013 (ten years after biologics began being approved to treat plaque psoriasis) the long-term treatment of psoriasis with biologic therapies was often compromised by adverse events, there remained a need for an improved, orally available therapy for the treatment of psoriasis that limits disease progression without impacting patient lifestyle and wellbeing. Trial Tr. at 941:25–943:15 (Gilmore Cross 6.21.21); 287:24-25, 291:13–14 (Alexis Direct 6.15.21).

799. Otezla met the need for a treatment for plaque psoriasis, particularly moderate plaque psoriasis, that is safer than prior art treatments, that is effective, and that lacks common barriers to adherence because Otezla has advantages over other treatments including its oral administration, its efficacy that is on-par with methotrexate, and its anti-inflammatory rather than immunosuppressant mechanism of action (owing to its inhibition of PDE4) that causes Otezla's very favorable safety profile and lack of laboratory monitoring or other restrictions on lifestyle. DTX-372 at DTX-372_6; Trial Tr. at 883:9–884:2, 944:7–18 (Gilmore Direct 6.21.21); 169:3–9 (Schafer Direct 6.14.21); 304:9–23, 305:5–306:24 (Alexis Direct 6.15.21).

800. Even Dr. Gilmore agreed that Otezla's oral dosing, lack of a lab-monitoring requirement, efficacy, safety and tolerability profile, and improved convenience compared with previously available options, positioned it as of 2012 to fill a gap in the management of psoriasis. Trial Tr. at 944:7–18 (Gilmore Cross 6.21.21).

801. Physician do not prescribe single attributes of a drug—they must find a treatment that, as a whole, is the best possible fit for a given patient accounting for multiple factors and the patient's specific circumstances. Trial Tr. at 303:23–304:8 (Alexis Direct 6.15.21).

802. Otezla's efficacy is similar to that of methotrexate. Trial Tr. at 879:10–880:14 (Gilmore Direct 6.21.21); DTX-367 at DTX-367_1.

803. Because Otezla is a PDE4 inhibitor it reduces excess inflammation without suppressing the immune system. Trial Tr. at 304:9–23 (Alexis Direct 6.15.21).

804. Otezla is the only PDE4 inhibitor approved for the treatment of psoriasis. Trial Tr. at 304:24–305:2 (Alexis Direct 6.15.21).

805. Otezla does not have black-box warnings, unlike the biologics, because it is not associated with risks of serious infections, and unlike methotrexate, Otezla is not associated with cancers, kidney or liver damage, or any other end-organ toxicities, and is not contraindicated for women of childbearing potential. Trial Tr. at 300:25–301:22 (Alexis Direct 6.15.21).

806. Otezla's prescribing information states that "Treatment of OTEZLA is associated with an increase in adverse reactions of depression," however the incidences seen in clinical trials were low, and instances of suicidal behavior were lower than in the placebo group. JTX-110 at JTX-110_3. Otezla's prescribing information also notes that most events of diarrhea, nausea, and vomiting occurred within the first weeks of treatment, and that patients who reduced dosage or discontinued Otezla generally improved quickly. JTX-110 at JTX-110_3.

807. Unlike biologics, Otezla is administered orally and therefore lacks the barriers to adherence associated with injectable treatments, or the messy and difficult-to-apply topical treatments. Trial Tr. at 300:25–301:2, 301:23–302:1 (Alexis Direct 6.15.21).

808. Unlike biologics and older oral systemics, Otezla does not require lab monitoring before beginning therapy or during therapy, and unlike methotrexate it does not require liver biopsies. Trial Tr. at 300:25–301:2, 302:2–5 (Alexis Direct 6.15.21).

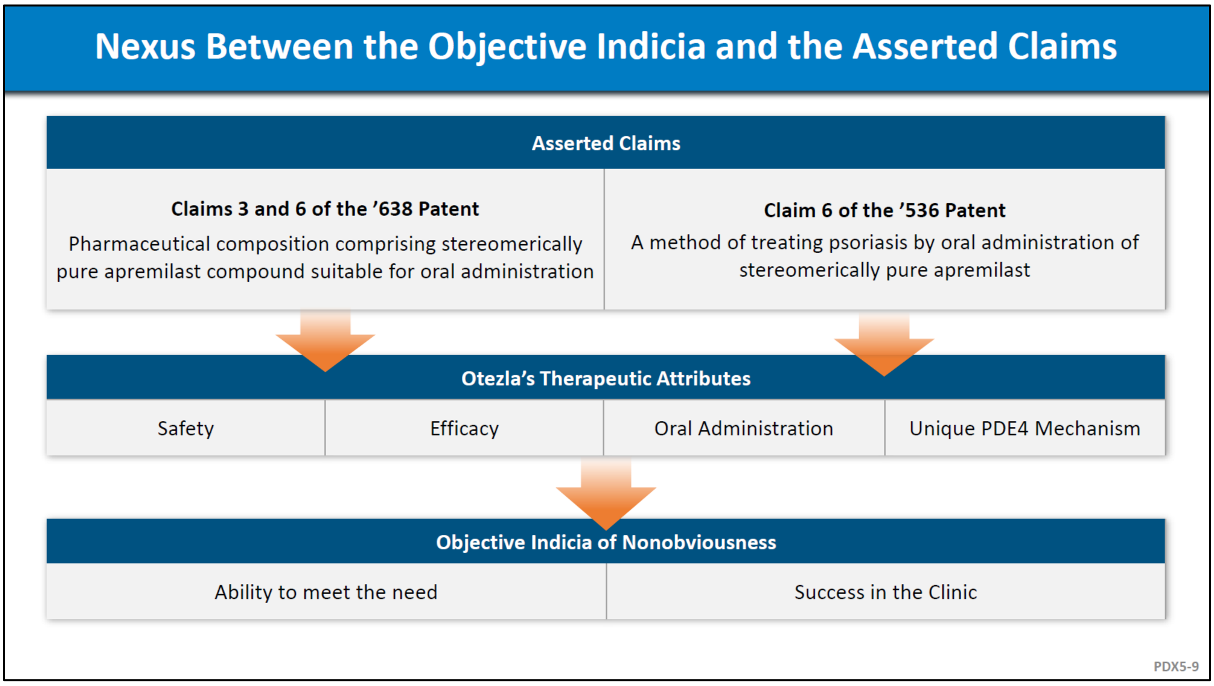
809. Patients taking Otezla do not need to abstain from drinking alcohol, or otherwise alter their lifestyle to continue treatment, which is required for patients taking acitretin and methotrexate. Trial Tr. at 300:25–301:2, 302:14–23 (Alexis Direct 6.15.21).

(4) A nexus exists between the asserted claims of the ’638 and ’536 Patents and the long-felt need for an improved psoriasis treatment.

810. The asserted claims of the ’638 Patent claim a pharmaceutical composition comprising stereomerically pure apremilast. JSF ¶¶ 26–31 (ECF No. 422).

811. The asserted claims of the ’536 Patent claim a method of treating psoriasis, which comprises orally administering to a patient having psoriasis, stereomerically pure apremilast. JSF ¶¶ 40–41 (ECF No. 422).

812. The asserted claims of the ’638 and ’536 Patents gave Otezla its safety profile, its efficacy, its oral route of administration, and its unique PDE4-inhibiting mechanism of action, which in turn allowed Otezla to meet the need for a treatment for plaque psoriasis, particularly moderate plaque psoriasis, that was safer than prior art treatments, that was effective, and that lacked common barriers to adherence. Trial Tr. at 310:7–311:22 (Alexis Direct 6.15.21); PDX5-9.



d) Skepticism

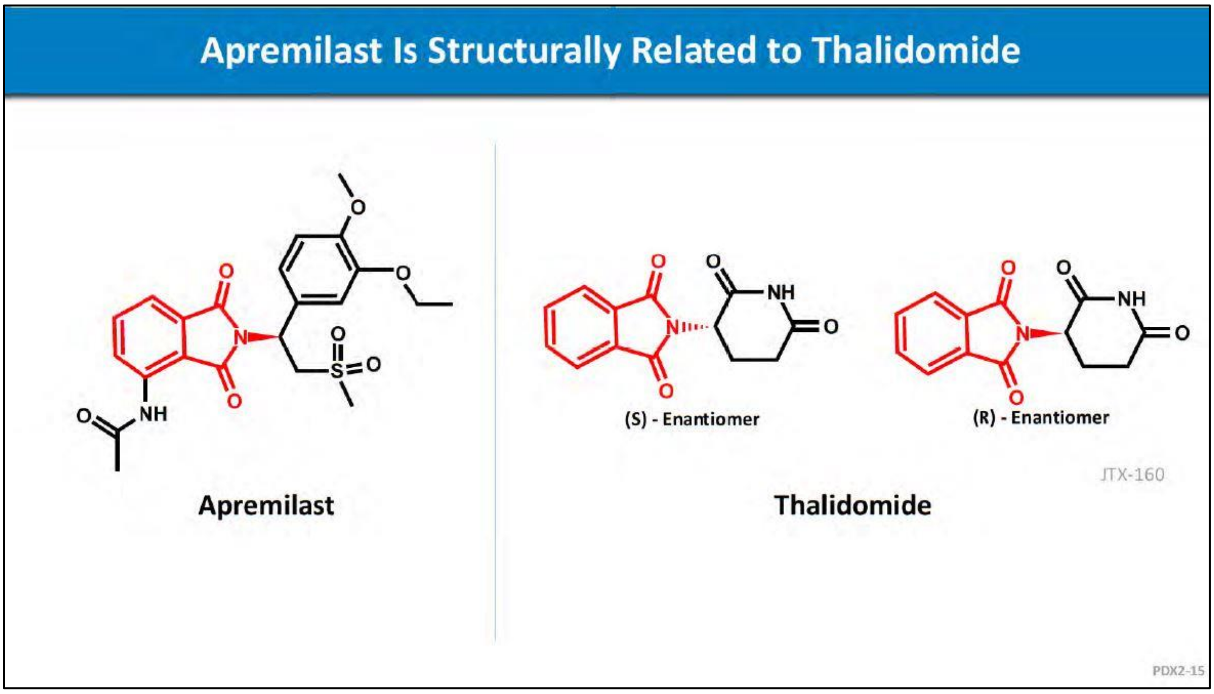
(1) Background

(a) Brief overview of thalidomide

813. The overview of thalidomide is incorporated by reference. PF ¶¶ 520–38.

(b) Apremilast's relationship to thalidomide

814. The structures of apremilast and thalidomide are related to each other in that they both contain a thalimido group. The shared thalimido group between apremilast and thalidomide are illustrated in the following demonstrative, PDX2-15, used with Dr. Davies's testimony. The thalimido group common to both molecules is highlighted in red. Trial Tr. at 103:1–11 (Davies Direct 6.14.21); JTX-160 at JTX-160_2.



815. The scientific community discovered the protein binding target of thalidomide in 2009 or 2010 (i.e., cereblon), which was considered a potential cause for thalidomide's teratogenicity. JTX-160 at JTX-160_7; Trial Tr. at 132:11–14 (Schafer Direct 6.14.21). Celgene did not know apremilast does not bind to cereblon until 2013. *See* JTX-210 at JTX-210_1, JTX-210_50.

(c) Celgene's clinical trials with SelCIDs were largely conducted in men.

816. Celgene tested CDC-801, the first SelCID to be studied in clinical trials, only in healthy male volunteers, because at the time, the safety of SelCIDs like CDC-801 was not yet clear due to concerns of possible teratogenicity. Trial Tr. at 161:20–162:6 (Schafer Direct 6.14.21); PTX-940 at PTX-940_68, PTX-940_70.

817. It is not typical to run Phase 1 studies in men only; typically, one would want to run Phase 1 studies in males and females to look at absorption and pharmacokinetic safety in both males and females. Trial Tr. at 162:7–11 (Schafer Direct 6.14.21).

818. Subsequent Phase 1 studies of CDC-801 were also conducted only in men. Trial Tr. at 162:12–19 (Schafer Direct 6.14.21); PTX-940 at PTX-940_70.

819. Celgene tested the second SelCID it put into clinical trials, CC-7085, in men and/or postmenopausal women or surgically sterilized women. Trial Tr. at 162:20–163:1 (Schafer Direct 6.14.21).

820. CC-7085 was never tested in women of childbearing age. Trial Tr. at 163:2–3 (Schafer Direct 6.14.21).

821. The first clinical trial for apremilast was conducted in healthy male and surgically sterile/post-menopausal female subjects. Trial Tr. at 163:4–7 (Schafer Direct 6.14.21); PTX-1267 at PTX-1267_58.

822. In the first Phase 2 psoriasis study for apremilast, while women of childbearing potential could be enrolled into the study, they "must have a negative urine pregnancy test at screening," and they must agree to use two forms of contraceptive methods. *See* PTX-1276 at PTX-1276_89; PTX-833 at PTX-833_2; Trial Tr. at 125:16–25 (Davies Redirect 6.14.21). Pregnant or lactating females were excluded from the study population. *See* PTX-1276 at PTX-1276_89.

(2) FDA's skepticism of apremilast's structure

823. FDA raised safety concerns about teratogenicity and racemization, thus expressing skepticism about apremilast's structural relationship to thalidomide. Trial Tr. at 97:15–23 (Davies Direct 6.14.21); PTX-833 at PTX-833_2.

824. Racemization refers to a chemical change in a molecule that causes an enantiomer to change into the other enantiomer. Trial Tr. at 98:2–9 (Davies Direct 6.14.21).

825. When racemization occurs in a pure enantiomer, it will eventually become a racemic mixture, a one-to-one mixture, of both enantiomers. Trial Tr. at 98:2–9 (Davies Direct 6.14.21).

826. FDA communicated its skepticism regarding apremilast's structural relationship to thalidomide in an August 24, 2004 fax providing a list of deficiencies in relation

to an Investigational New Drug Application ("IND") that Celgene submitted for its compound CC-10004. PTX-833 at PTX-833_2; Trial Tr. at 99:18–100:15 (Davies Direct 6.14.21).

827. An IND is an application that a company submits to FDA that summarizes the safety and the pharmacology and is required prior to starting a clinical trial. Trial Tr. at 100:5–9 (Davies Direct 6.14.21); 163:10–16 (Schafer Direct 6.14.21).

828. After an IND is submitted, the FDA has 30 days to review the application and if there are any problems, it can issue a clinical hold within that time frame. Trial Tr. at 164:4–9 (Schafer Direct 6.14.21).

829. If the FDA raises no concerns within 30 days following the submission of an IND, the company may proceed with the start of the trial. Trial Tr. at 164:10–14 (Schafer Direct 6.14.21); *see also id.* at 164:13–14 (Schafer Direct 6.14.21) ("Q. So it's sort of a 'no news is good news' type of thing? A. Yes.").

830. If FDA raises concerns, it will provide correspondence, which will include issues that FDA wants to discuss, usually pertaining to safety, which will need to be addressed before the trial can proceed. Trial Tr. at 164:15–20 (Schafer Direct 6.14.21).

831. CC-10004 was Celgene's name for apremilast. Trial Tr. at 100:3–4 (Davies Direct 6.14.21).

832. Celgene submitted its IND for the treatment of psoriasis on July 28, 2004. Trial Tr. at 100:22–25 (Davies Direct 6.14.21); 163:10–164:20 (Schafer Direct 6.14.21); PTX-1267 at PTX-1267_1–5.

833. Compared to leprosy, which can be life-threatening and lacks treatment options, psoriasis is a less terrible and severe disease. Trial Tr. at 104:20–105:5 (Davies Direct 6.14.21).

834. On August 24, 2004, FDA requested additional information from Celgene regarding "possible structural similarities of CC-10004 to thalidomide," and "[t]he fate of the

metabolites of the parent drug, their potential for teratogenicity" and the half-lives of the metabolites of the parent drug. PTX-833 at PTX-833_2–3.

835. In particular, FDA was concerned that apremilast would be toxic and teratogenic and that it would racemize *in vivo* and that the resultant racemic mixture would be toxic and teratogenic in the body, and that this effect may not be discovered until human studies. PTX-833 at PTX-833_2–3; Trial Tr. at 101:6–16; 106:10–16 (Davies Direct 6.14.21). ("So the FDA's worried that apremilast, like thalidomide, may cause severe toxicity, particularly birth defects. And that apremilast, like thalidomide, may racemize in the body and that the resulting mixture—the racemic mixture, which would contain the opposite enantiomer may cause toxicity, particularly birth defects. And the toxicity may not be discovered until human studies.").

836. It was not possible to know whether apremilast would racemize just by looking at apremilast's structure. Trial Tr. at 106:18–24 (Davies Direct 6.14.21). The only way to determine whether apremilast would racemize in the body would be to do an experiment. Trial Tr. at 106:18–24 (Davies Direct 6.14.21).

837. Celgene responded to FDA's comments during teleconferences held on August 25, 26, and 27, 2004. Trial Tr. at 107:4–13 (Davies Direct 6.14.21); JTX-281.

838. Celgene's comments to FDA and FDA's responses were memorialized in an internal Celgene memorandum dated September 15, 2004. JTX-281; Trial Tr. at 107:4–13 (Davies Direct 6.14.21) ("This [JTX-281] is a copy of a memo from -- from Celgene describing the response and interactions with the FDA in teleconferences on August the 25th, 26th, and 27th of 2004. Q. And how does this memo relate to the fax we saw at PTX-833? A. This is addressing the questions, the safety concerns that the FDA put in that document.").

839. To address FDA's teratogenicity concerns, Dr. Muller, one of the named inventors of the '638 Patent, explained that apremilast lacks a glutarimide ring, a key

pharmacophore for thalidomide analogs, and Celgene confirmed "that the data collected to date had shown no teratogenic effects [of apremilast]." JTX-281 at JTX-281_3; Trial Tr. at 107:14–108:13 (Davies Direct 6.14.21).

840. A pharmacophore is a part of a molecule that is thought to be at least in part responsible for the effect that the molecule has on a receptor within the body, and is at least partly responsible for the observed biological effect. Trial Tr. at 108:16–22 (Davies Direct 6.14.21).

841. FDA also requested additional information as to Celgene's selection of the S-enantiomer of apremilast for clinical trials and inquired as to whether either enantiomer was expected to be more teratogenic than the other, as in thalidomide. PTX-833 at PTX-833_2–3.

842. Dr. Muller explained that apremilast's "chiral center was not acidic and thus was not readily racemizable like the chiral center found in thalidomide," and that apremilast "was not expected to racemize." JTX-281 at JTX-281_3; *see also* Trial Tr. at 107:14–108:13 (Davies Direct 6.14.21).

843. At least one of the reviewers of Celgene's IND for CC-10004 (apremilast) was a chemist, and that chemist raised the concerns reflected in FDA's August 24, 2004 fax to Celgene. Trial Tr. at 108:23–25, 109:9–13 (Davies Direct 6.14.21) ("Q. Now, let's look at the final sentence. What do you understand FDA to mean when they said that they would convey them, meaning Celgene's responses, to the chemist? . . . A. So what this indicates is that at least one of the reviewers was a chemist and that a chemist would be the person who raised these concerns and that they were going to convey back to the chemist the answer -- the responses that Celgene had produced.").

844. Based on FDA's interactions with Celgene as reflected in PTX-833 and JTX-281, that FDA was skeptical that it would be safe to administer apremilast to human beings in

a clinical trial and had some doubts about Celgene's IND and the apremilast compound. Trial Tr. at 114:1–115:3 (Davies Cross 6.14.21).

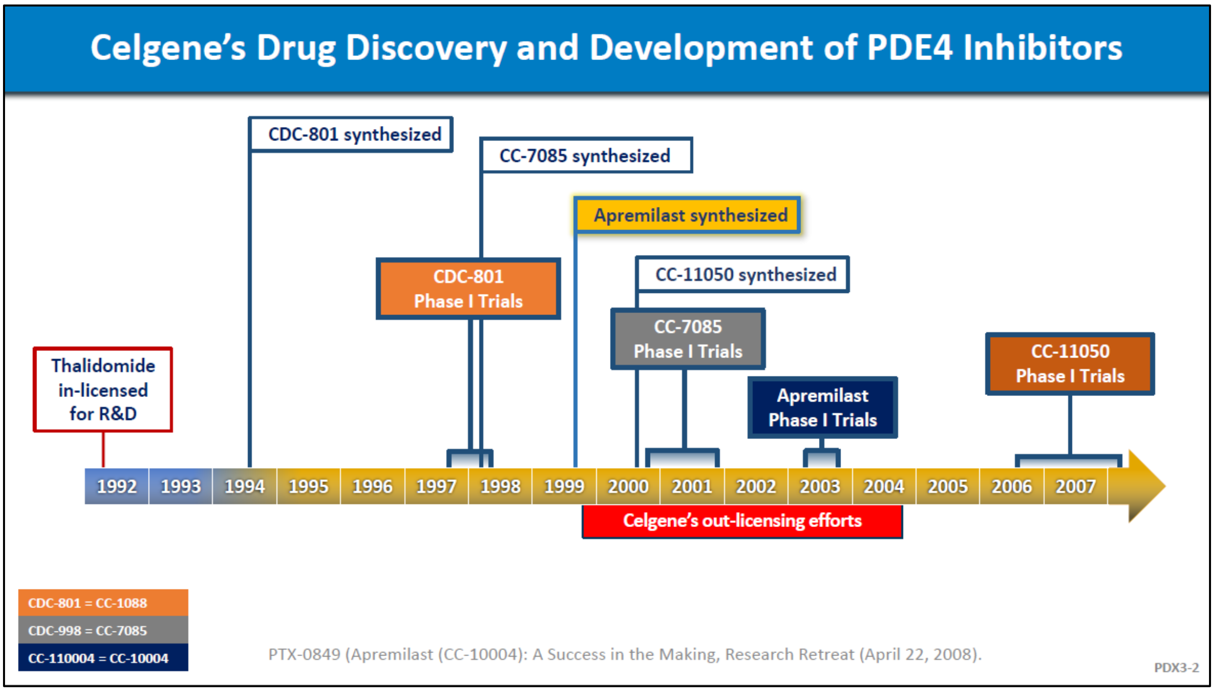
845. That the FDA appeared satisfied with Dr. Muller's explanation does not mean that the FDA was not skeptical of apremilast's structural relationship to thalidomide, and the potential harm apremilast may cause. JTX-281 at JTX-281_3; Trial Tr. at 122:9–14 (Davies Cross 6.14.21).

846. As part of the discussion with FDA, FDA instructed Celgene to require women of childbearing age to use two forms of birth control. PTX-833 at PTX-833_2; Trial Tr. at 125:16–25 (Davies Redirect 6.14.21).

847. FDA was skeptical about whether apremilast should go into a clinical trial based on the concerns that FDA raised regarding the structural similarities between apremilast and thalidomide and apremilast's potential for teratogenicity based upon those structural similarities, regardless of whether FDA used the word "skepticism" or "skeptical." Trial Tr. at 115:16–22 (Davies Cross 6.14.21) ("Q. . . . The FDA doesn't say it's skeptical in making these requests for information, does it? A. Well, it's asking about -- it's -- it's obviously worried about structural similarities between apremilast and thalidomide. It's also worried about the enantiomers and which enantiomer and the potential for teratogenicity. That's skeptical about whether this should go into a clinical trial."); 116:19–24 (Davies Cross 6.14.21) ("I think it's clear what the FDA is saying. They're concerned about a similarity between apremilast and thalidomide and the enantiomers as in thalidomide.").

(3) Skepticism of apremilast through failure to license

848. Between early 1999 and 2004, Celgene attempted to out-license its SelCID program, including apremilast. Trial Tr. at 164:21–165:5 (Schafer Direct 6.14.21); PDX3-2.



849. Dr. Schafer was involved in these out-licensing activities between 1999 and 2004, for which he prepared and delivered presentations to other companies. Trial Tr. at 165:6–13, 134:19–25, 149:19–25, 166:1–167:3 (Schafer Direct 6.14.21); PTX-940; JTX-208; PTX-943.

850. The reason Celgene sought to out-license its SelCID program in the 1999–2004 timeframe was because "Celgene was a small company" and it "[was] not able to really perform this drug development [of SelCIDs] on its own." Trial Tr. at 164:21–165:25 (Schafer Direct 6.14.21).

851. Celgene was not able to perform the drug development of SelCIDs on its own because clinical development is expensive, due to "the number of years, number of trials, the number of subjects that have to be treated in order to prove that a drug is safe and efficacious." Trial Tr. at 165:14–25 (Schafer Direct 6.14.21).

852. Celgene approached 11 different companies about licensing SelCIDs and apremilast: Aventis, BI, GSK, BMS, Wyeth, Amgen, Pharmacia, Roche, Sankyo, Lilly and

Forest. Trial Tr. at 166:25–167:3, 167:13–18 (Schafer Direct 6.14.21); JTX-210 at JTX-210_44.

853. If one of Aventis, BI, GSK, BMS, Wyeth, Amgen, Pharmacia, Roche, Sankyo, Lilly or Forest had licensed apremilast, "they could have developed it for the treatment of inflammatory diseases" and "could have built up . . . the clinical plan, any type of work that needed to be done on the drug substance formulations, all of that work." Trial Tr. at 167:21–168:10 (Schafer Direct 6.14.21). In other words, if any of the companies agreed to take the license from Celgene, they would have been able to make pharmaceutical compositions comprising apremilast, and develop methods of treatment using apremilast. Trial Tr. at 168:5–10 (Schafer Direct 6.14.21).

854. Both GSK and Lilly tested apremilast in their labs. JTX-210 at JTX-210_44.

855. None of Aventis, BI, GSK, BMS, Wyeth, Amgen, Pharmacia, Roche, Sankyo, Lilly or Forest took a license to Celgene's SelCIDs. Trial Tr. at 166:25–167:20 (Schafer Direct 6.14.21).

(4) GlaxoSmithKline's skepticism of apremilast

856. GlaxoSmithKline ("GSK") was also skeptical about apremilast's relationship to thalidomide. *See* PF ¶¶ 857–69.

857. GSK evaluated apremilast and a few other compounds from Celgene as part of an in-licensing opportunity. Trial Tr. at 228:15–24 (Knowles Direct 6.15.21).

858. Celgene provided to GSK *in vitro* testing on apremilast. Trial Tr. at 229:6–11 (Knowles Direct 6.15.21).

859. As part of its analysis of apremilast, GSK ran assessments to derive efficacy and therapeutic index data, using a ferret model. Trial Tr. at 228:25–230:11 (Knowles Direct 6.15.21). *See* PF ¶¶ 254–59, 876–97.

860. Apremilast was outstanding in the ferret model, with a much higher therapeutic index than any of the other compounds GSK looked at. Trial Tr. at 230:9–11 (Knowles Direct 6.15.21).

861. The therapeutic index of apremilast was 31 times higher than GSK's own compound, cilomilast. Trial Tr. at 230:12–17 (Knowles Direct 6.15.21).

862. Dr. Knowles, who was personally involved in evaluating apremilast, Trial Tr. at 228:15–24 (Knowles Direct 6.15.21), gave his views to senior management that the potency, selectivity, cellular effects, efficacy *in vivo*, therapeutic index in ferrets and other properties that were then known were all very promising for an anti-inflammatory drug to be given by the oral route for systemic effects. Trial Tr. at 230:24–231:10 (Knowles Direct 6.15.21).

863. Dr. Knowles recommended to senior management that GSK continue working with Celgene and consider in-licensing it. Trial Tr. at 230:24–231:5 (Knowles Direct 6.15.21).

864. The senior management that considered his proposal included "drug discoverers"—scientists and clinical scientists—in addition to commercial people. Trial Tr. at 231:7–17 (Knowles Direct 6.15.21).

865. The late development scientists and the commercial people had the point of view that apremilast's connection with thalidomide was "extremely unhelpful," and spoke of a risk that apremilast might also be teratogenic like thalidomide. Trial Tr. at 231:19–232:1 (Knowles Direct 6.15.21).

866. The late development scientists and the commercial people also expressed concern that developing apremilast would involve reputational risks because of the strong link between thalidomide and apremilast, including their shared structural element. Trial Tr. at 231:19–232:1 (Knowles Direct 6.15.21).

867. Senior management at GSK, eventually along with Dr. Knowles, shared the concern expressed by the late development scientists and the commercial people about the

relationship between apremilast and thalidomide. Trial Tr. at 232:2–6 (Knowles Direct 6.15.21).

868. As a result of these discussions, Professor Knowles was convinced that advancing with apremilast would pose a significant risk to GSK. Trial Tr. at 232:2–6 (Knowles Direct 6.15.21).

869. GSK declined the apremilast in-licensing opportunity. Trial Tr. at 232:7–9 (Knowles Direct 6.15.21).

(5) A nexus exists between the asserted claims of the ’638 and ’536 Patents and the skepticism of apremilast.

870. The asserted claims of the ’638 Patent claim a pharmaceutical composition comprising stereomerically pure apremilast. JSF ¶¶ 26–31 (ECF No. 422).

871. The asserted claims of the ’536 Patent claim a method of treating psoriasis, which comprises orally administering to a patient having psoriasis, stereomerically pure apremilast. JSF ¶¶ 40–41 (ECF No. 422).

872. The skepticism of the FDA and other pharmaceutical companies concerned whether apremilast could be safely developed as a pharmaceutical composition, and whether it could be a suitable treatment for a disease like psoriasis, and was thus directed at the workability of the asserted claims. PTX-833 at PTX-833_2–3; Trial Tr. at 100:22–25, 101:6–16, 106:10–16, 104:20–105:5 (Davies Direct 6.14.21); 163:10–164:20 (Schafer Direct 6.14.21); PTX-1267.

e) Unexpected results

(1) Cilomilast is the proper point of comparison for unexpected results.

873. In both 1999 and 2002, cilomilast was the most advanced PDE4 inhibitor in terms of clinical development. Trial Tr. at 234:12–15 (Knowles Direct 6.15.21).

874. As of 1999 or 2002, the POSA would have compared apremilast to cilomilast, because cilomilast was considered the gold standard against which all other PDE4 inhibitors should be compared. Trial Tr. at 233:6–13; 233:23–234:6; 234:12–20 (Knowles Direct 6.15.21); JTX-142 at JTX-142_4; JTX-282 at JTX-282_2.

875. As of 1999 or 2002, the POSA would not have compared apremilast to the racemic compound in Example 12 of the '358 Patent, because there was no data in the patent or the prior art to give the POSA any reason to look at Example 12 as opposed to cilomilast or any number of other compounds with data. Trial Tr. at 234:21–235:1 (Knowles Direct 6.15.21); DTX-174.

(2) Apremilast demonstrated an unexpectedly superior therapeutic index for emesis in ferrets compared to cilomilast.

876. Apremilast shows an unexpectedly better therapeutic index than cilomilast as it relates to emesis. Trial Tr. at 155:16–160:3 (Schafer Direct 6.14.21); 236:8–237:1 (Knowles Direct 6.15.21); PTX-374; JTX-118; JTX-208 at JTX-208_43–45.

877. A therapeutic index is the difference in dose for a drug between its efficacy and its safety or tolerability. Trial Tr. at 158:4–19 (Schafer Direct 6.14.21); 207:4–25 (Knowles Direct 6.15.21); 250:1–3 (Knowles Cross 6.15.21); 729:15–25 (Page Direct 6.18.21).

878. A therapeutic index does not evaluate the difference between an efficacious dose and the entire side effect profile of a drug; such a concept does not exist. Trial Tr. at 250:4–12 (Knowles Cross 6.15.21); 267:21–24 (Knowles Redirect 6.15.21).

879. A therapeutic window is a "closely related concept" to a therapeutic index in that "it's looking at . . . over what range one can get a beneficial effect, an efficacious effect, without reaching tolerability criteria." Trial Tr. at 208:10–17 (Knowles Direct 6.15.21).

880. Therapeutic index or therapeutic window is a measure frequently relied upon by scientists to gauge the drug's comparative efficacy and toxicity or tolerability. JTX-166 at JTX-166_2; JTX-137 at JTX-137_10–11.

881. One wants the window or index, to be as large as possible for a given compound. Trial Tr. at 158:4–19 (Schafer Direct 6.14.21); 207:14–25, 208:1–9 (Knowles Direct 6.15.21). With a therapeutic index, the goal is to get well above 1. Trial Tr. at 208:4–6, 230:18–19 (Knowles Direct 6.15.21).

882. The most common side effects associated with PDE4 inhibitors as of 1999 were the side effects of nausea and emesis. Trial Tr. at 250:21–251:1 (Knowles Cross 6.15.21); 268:6–13 (Knowles Redirect 6.15.21); JTX-67 at JTX-67_7. ("The development of drugs of this class has been hampered by adverse events, particularly nausea and emesis"); JTX-114 at JTX-114_2.

883. In 2001, Celgene, in collaboration with GlaxoSmithKline, evaluated apremilast and a few other compounds in a ferret lung neutrophilia and emesis model. Trial Tr. at 156:25–157:5, 158:25–159:13 (Schafer Direct 6.14.21); PTX-374; JTX-118. This confidential data was not available to the public and would not have been available to a POSA in 1999-2002. Trial Tr. at 234:21–235:6 (Knowles Direct 6.15.21).

884. A ferret lung neutrophilia and emesis model is a study in which one can measure both anti-inflammatory effect in the lung of the ferret and the vomiting, or emesis, of the ferret. Trial Tr. at 157:11–23 (Schafer Direct 6.14.21); 229:12–25, 235:20–236:7 (Knowles Direct 6.15.21); 727:14–729:14 (Page Direct 6.18.21).

885. Dr. Page has used a ferret model himself to evaluate emesis of PDE4 inhibitors. Trial Tr. at 779:15–780:10 (Page Cross 6.18.2021); JTX-232 at JTX-232_3.

886. Before companies started using the ferret model to assess whether a PDE4 inhibitor showed emesis "you were going to people before you found out you had a problem." Trial Tr. at 778:1–779:14 (Page Cross 6.18.21).

887. Therapeutic indices, like those established in the ferret lung neutrophilia and emesis model, are used to estimate doses in humans. Trial Tr. at 159:14–20 (Schafer Direct 6.14.21); 269:16–270:4 (Knowles Redirect 6.15.21).

888. The therapeutic index in emesis "gives some early indication of potential toxicity." Trial Tr. at 736:17–23 (Page Direct 6.18.21); *see also* JTX-232 at JTX-232_7.

889. Ferrets are used to test emesis because ferrets, unlike rats and mice, have the capacity to retch. Trial Tr. at 230:2–8 (Knowles Direct 6.15.21). It is not possible to evaluate a drug for a therapeutic index for nausea, because there was not, and is not, a validated animal model that assesses the side effect of nausea. Trial Tr. at 731:9–18 (Page Direct 6.18.21); 268:14–24 (Knowles Direct 6.15.21)

890. When apremilast was tested in the ferret lung neutrophilia and emesis model, it showed efficacy at 0.8 mg/kg, and induced emetic behavior at 10 mg/kg, providing a therapeutic index of 12. Trial Tr. at 158:2–11 (Schafer Direct 6.14.21); 728:23–729:23 (Page Direct 6.18.21) (calculating therapeutic index as 12.5); PTX-374 at PTX-374_15; JTX-118 at JTX-118_15.

891. In contrast, when cilomilast was tested in the ferret lung neutrophilia and emesis model, it showed efficacy at 8 mg/kg—which is 10 fold less potent than apremilast—and showed emesis at 3 mg/kg, providing a therapeutic index of 0.38. Trial Tr. at 158:4–19 (Schafer Direct 6.14.21); PTX-374 at PTX-374_15; JTX-118 at JTX-118_15.

892. Other proprietary Celgene SelCIDs, tested in the same ferret lung neutrophilia and emesis model, were not as good as apremilast. Trial Tr. at 158:25–159:4 (Schafer Direct 6.14.21); PTX-374 and PTX-374 at PTX-374_15; JTX-118 at JTX-118_15.

893. Apremilast's therapeutic index had a better than 30-fold difference from the therapeutic index of cilomilast in the same model. Trial Tr. at 158:12–19, 158:21–160:3 (Schafer Direct 6.14.21); 236:14–19 (Knowles Direct 6.15.21).

894. The data from the ferret lung neutrophilia and emesis model confirmed the data acquired from the PDE4A4 ratio analysis. Trial Tr. at 159:5–13 (Schafer Direct 6.14.21).

895. That apremilast's therapeutic index had a 31-fold difference from the therapeutic index of cilomilast in the same model was a "thrilling" result for the Celgene scientists, including Dr. Schafer, because it showed that Celgene had something that was much better than cilomilast, which had been taken into Phase 3 trials for chronic obstructive pulmonary disease. Trial Tr. at 159:21–160:3 (Schafer Direct 6.14.21); 236:15–19 (Knowles Direct 6.15.21).

896. That apremilast had a 31-fold improvement over cilomilast would have been "most unexpected." Trial Tr. at 236:20–22 (Knowles Direct 6.15.21).

897. Dr. Knowles is aware of no other PDE4 inhibitor intended for systemic administration with a similar-to-apremilast therapeutic index for emesis. Trial Tr. at 236:23–237:1 (Knowles Direct 6.15.21).

(3) Apremilast demonstrated an unexpectedly superior PDE4A4 ratio compared to cilomilast and CC-7085 indicating potential for an improved side effect profile.

898. Apremilast was known internally at Celgene as CC-10004, or CC-110004. Trial. Tr. at 100:3–4 (Davies Direct 6.14.21); 145:2–6 (Schafer Direct 6.14.21).

899. In studies conducted by Celgene, apremilast showed an unexpectedly improved PDE4A4 ratio over Ariflo (cilomilast) and CC-7085. Trial Tr. at 151:10–153:17 (Schafer Direct 6.14.21), JTX-208 at JTX-208_14, JTX-208_37. This confidential data was not available to the public and would not have been available to a POSA in 1999-2002. Trial Tr. at 234:21–235:6 (Knowles Direct 6.15.21).

900. PDE4A4 is one of the isoforms of PDE4. Trial Tr. at 150:17–18 (Schafer Direct 6.14.21).

901. A PDE4 isoform is one of the 25 different types of PDE4 proteins in the human body. Trial Tr. at 150:19-22 (Schafer Direct 6.14.21).

902. Celgene was interested in PDE4A4 ratios because its scientists believed that the ratio of binding to the low affinity versus high affinity isoforms could predict the side effects of nausea and emesis. Trial Tr. at 150:23–151:3 (Schafer Direct 6.14.21)

903. Celgene was looking for a PDE4A4 ratio that was low. Trial Tr. at 151:6–9 (Schafer Direct 6.14.21).

904. Apremilast had a very low PDE4A4 ratio of 0.15. Trial Tr. at 151:12–16 (Schafer Direct 6.14.21); JTX-208 at JTX-208_14.

905. Apremilast's PDE4A4 ratio of 0.15 was a good result, which predicted better tolerability in humans. Trial Tr. at 237:6–19 (Knowles Direct 6.15.21).

906. In contrast to the PDE4A4 ratio for apremilast, Ariflo (cilomilast) had a PDE4A4 ratio of 1.84. Trial Tr. at 151:10–17, 152:1–2 (Schafer Direct 6.15.21); JTX-208 at JTX-208_14.

907. Cilomilast was one of the two PDE4 inhibitors that had made it furthest in clinical development, in that it had advanced to Phase 3 trials by 1999. Trial Tr. at 152:9–14 (Schafer Direct 6.14.21); JTX-67 at JTX-67_5; JTX-142 at JTX-142_4.

908. Apremilast had a PDE4A4 ratio that was more than ten times lower than cilomilast's. Trial Tr. at 151:10–17, 152:15–18 (Schafer Direct 6.14.21).

909. Apremilast also had a PDE4A4 ratio (0.15) that was more than 10 times lower than that of CC-7085, the racemic compound (1.67). Trial Tr. at 151:10–17, 153:9–10 (Schafer Direct 6.14.21); JTX-208 at JTX-208_37.

910. Apremilast's PDE4A4 ratio was among the best of about 17 compounds tested. Trial Tr. at 153:11–17 (Schafer Direct 6.14.21); JTX-208 at JTX-208_37.

911. Celgene was very excited and very happy with this data, and to be getting such a low PDE4A4 ratio for apremilast. Trial Tr. at 153:11–17 (Schafer Direct 6.14.21).

912. The lower PDE4A4 ratio of apremilast, as compared to Example 12 (CC-7085) would have been unexpected, as there was no data to provide the POSA or anyone else to think that might be the result. Trial Tr. at 237:10–15 (Knowles Direct 6.15.21).

(4) Apremilast demonstrated an unexpectedly superior potency over CC-7085 in the *in vivo* murine shock model.

913. Celgene tested apremilast and CC-7085 in a murine shock model, which examines efficacy in a mouse lipopolysaccharide-induced serum TNFα inhibition model. Trial Tr. at 154:9–14 (Schafer Direct 6.14.21); JTX-114 at JTX-114_18. This confidential data was not available to the public and would not have been available to a POSA in 1999-2002. Trial Tr. at 234:21–235:6 (Knowles Direct 6.15.21).

914. The murine shock model is "a really complicated system where the compound has to be absorbed from the oral dose . . . has to reach the site of action in the body through the blood . . . [and] has to be not cleared so fast that there is no time for it have its effect." Trial Tr. at 239:9–19 (Knowles Direct 6.15.21).

915. Apremilast was unexpectedly more potent over CC-7085 in the murine shock model as presented in internal data to Celgene. Trial Tr. at 154:9–155:15 (Schafer Direct 6.14.21); 240:11–13 (Knowles Direct 6.15.21). CC-7085 is the racemic compound that was later identified in Example 12 of the '358 Patent. Trial Tr. at 1370:19–23 (Davies Direct 6.23.21).

916. The data for the murine shock model study are reported in internal Celgene documents as ED_{50} values. JTX-114 at JTX-114_18, JTX-114_20.

917. ED_{50} values are the 50 percent efficacious dose, which means, in the context of the murine shock model study, it is the dose that reduces 50 percent of the TNFα production in the mouse. Trial Tr. at 154:15–18 (Schafer Direct 6.14.21).

918. In the context of the murine shock model study, the scientists were looking for a low ED_{50} value. Trial Tr. at 154:19–21 (Schafer Direct 6.14.21).

919. In the murine shock model study, apremilast had an ED_{50} value of 0.05 mg/kg. Trial Tr. at 154:23–25 (Schafer Direct 6.14.21); JTX-114 at JTX-114_18, JTX-114_20.

920. The fact that apremilast had "really good potency in [the murine shock] model" shows that all of the steps required in the mouse's "complicated system" to move the compound from administration to the site of action have been met. Trial Tr. at 239:9–19 (Knowles Direct 6.15.21).

921. The murine shock model can be used to predict a dose range which would be effective in human studies. Trial Tr. at 239:14–19 (Knowles Direct 6.15.21).

922. In contrast to apremilast's ED_{50} value in the murine shock model study, CC-7085 had an ED_{50} value of 1 mg/kg. JTX-114 at JTX-114_18, JTX-114_20.

923. Apremilast was 20-fold more potent than the racemate CC-7085 in the murine shock model. Trial Tr. at 154:23–25 (Schafer Direct 6.14.21); JTX-114 at JTX-114_18, JTX-114_20; see also JTX-208 at JTX-208_41.

924. A 20-fold difference, like that shown between apremilast and CC-7085 (an enantiomer and its racemate) in the murine shock model test, is a very big difference. Trial Tr. at 155:3–15 (Schafer Direct 6.14.21).

925. The 20-fold difference in potency between apremilast and CC-7085 was unexpected, because the maximum difference one would expect between a racemate (like CC-7085) and its enantiomer (like apremilast) is 1 to 0.5 mg/kg, assuming that one enantiomer is

completely inactive. Trial Tr. at 239:22–240:8, 240:11–13 (Knowles Direct 6.15.21); 155:3–15 (Schafer Direct 6.14.21).

926. Such a big difference in potency between apremilast and CC-7085 suggests that the R-enantiomer is blocking the effect of the S-enantiomer (apremilast) in some way. Trial Tr. at 239:22–240:8 (Knowles Direct 6.15.21).

927. The POSA as of 1999 or 2002 would not have expected a 20-fold difference in potency between apremilast and CC-7085. Trial Tr. at 240:11–13 (Knowles Direct 6.15.21).

928. That apremilast was 20-fold more potent than the racemate CC-7085 in the murine shock model was very surprising to the scientists at Celgene, including Dr. Schafer; they did not expect a 20-fold difference in potency between the two molecules (which are an enantiomer and its racemate). Trial Tr. at 155:1–15 (Schafer Direct 6.14.21); *see also id.* at 240:11–13 (Knowles Direct 6.15.21) ("Q. Would the POSA in 1999 or 2002 have expected a 20-fold difference between these two compounds? A. No, they wouldn't.").

(5) Apremilast demonstrated an unexpectedly superior aqueous solubility over CC-7085.

929. Apremilast was unexpectedly more soluble in water than CC-7085. JTX-3 at 26:50–67. The solubility of apremilast was 0.012 mg/mL, while the solubility of CC-7085 was 0.0034 mg/mL, which is nearly a 30 fold difference. *Id.*

(6) A nexus exists between the asserted claims of the '638 and '536 Patents and the unexpected results.

930. The asserted claims of the '638 Patent claim a pharmaceutical composition comprising stereomerically pure apremilast. JSF ¶¶ 26–31 (ECF No. 422).

931. The asserted claims of the '536 Patent claim a method of treating psoriasis, which comprises orally administering to a patient having psoriasis, stereomerically pure apremilast. JSF ¶¶ 40–41 (ECF No. 422).

932. The asserted claims of the ’638 and ’536 Patents allowed apremilast to deliver unexpectedly improved potency and safety over the most advanced PDE4 inhibitors as of 1999 and 2002, and to fill a substantial need in patients who have psoriasis and other inflammatory diseases. Trial Tr. at 219:8–220:15 (Knowles Direct 6.15.21).

f) Otezla is a clinical success.

933. Otezla has achieved success in the clinic because it is a widely used and transformative treatment for moderate to severe plaque psoriasis. Trial Tr. at 305:7–16 (Alexis 6.15.21). Prior to Otezla, there was a patient population that was undertreated because these patients were caught in the middle between a set of therapies that were not sufficiently effective, and therapies that carried safety concerns or that patients were not comfortable using. Trial Tr. at 305:17–306:4 (Alexis Direct 6.15.21).

934. Due to Otezla’s safety profile, which is very favorable, dermatologists can give an effective therapy to more patients, including patients with preexisting disorders for whom other treatments would pose unacceptable risks. Trial Tr. at 305:7–12, 306:8–16 (Alexis Direct 6.15.21).

935. The lack of lab-monitoring requirements for Otezla is extremely helpful for patients, and allows them to avoid the burdensome bloodwork requirements associated with certain other therapies. Trial Tr. at 305:7–12, 306:17–21 (Alexis Direct 6.15.21).

936. In general, patients prefer an oral route of administration over topical or injectable treatments. Trial Tr. at 305:7–12, 306:22–24 (Alexis Direct 6.15.21).

937. As a result of Otezla allowing prescribers to offer an effective treatment that is easier to use and safer than many of the prior art therapies, patients can get relief from the potentially debilitating effects of psoriasis without resorting to treatment options that have more serious safety risks or barriers to adherence, or being undertreated. Trial Tr. at 306:25–307:25 (Alexis Direct 6.15.21).

938. Otezla patients are grateful for the improvement that Otezla can offer them, and describe how the drug has allowed them to be more comfortable in social and professional situations. Trial Tr. at 306:25–308:8 (Alexis Direct 6.15.21).

939. Although dermatologists have continued to prescribe the older oral systemic treatments even after Otezla was approved, that happens less frequently because Otezla offers a safer option that is effective and lacks barriers to adherence, whereas prescriptions for the older oral systemics are generally driven by cost or insurance considerations. Trial Tr. at 309:11–20 (Alexis Direct 6.15.21). Were it not for cost or payer barriers, Otezla would be the oral drug of choice for moderate to severe plaque psoriasis patients. Trial Tr. at 309:21–310:2 (Alexis Direct 6.15.21).

940. Defendants did not present any evidence showing that a significant number of patients or health care providers prefer methotrexate or biologics to Otezla because those drugs are dosed less frequently than Otezla.

941. Dr. Alexis and his colleagues have had positive experiences using Otezla to treat patients with psoriasis. Trial Tr. at 308:14–22 (Alexis Direct 6.15.21). Dr. Alexis has also had positive experiences using Otezla to treat patients who have both psoriasis and psoriatic arthritis, and that Otezla's ability to treat both joint involvement and skin disease is clearly beneficial to those patients. Trial Tr. at 308:23–309:10 (Alexis Direct 6.15.21).

942. Defendant's expert Dr. Gilmore agreed that there are patients who benefit from using Otezla, and prescribes Otezla to her patients whose disease is too severe for topical therapy, but who prefer an oral therapy or are uninterested in pursuing treatment with biologics. Trial Tr. at 876:8–22 (Gilmore Direct 6.21.21).

943. Dr. Gilmore agreed that Otezla has had some success in the clinic, that she prescribes Otezla to 5 to 10 percent of her psoriasis patients, and that 1 to 2 dozen of her patients have been on Otezla for more than a year. Trial Tr. 934:19–935:15 (Gilmore 6.21.21). Dr.

Gilmore's opinion that Otezla is not a success in the clinic is based solely on her personal "feeling" that Otezla's success in the clinic has not been "substantial." Trial Tr. at 935:16-25 (Gilmore Cross 6.21.21). When asked if 1.7 million Otezla prescriptions would qualify as a substantial success in the clinic, Dr. Gilmore admitted that she was neither aware of these prescription numbers nor did she have a "sense" of them. Trial Tr. at 936:7-14 (Gilmore 6.21.21).

(1) A nexus exists between the asserted claims of the '638 and '536 Patents and Otezla's clinical success.

944. The asserted claims of the '638 Patent claim a pharmaceutical composition comprising stereomerically pure apremilast. JSF ¶¶ 26–31 (ECF No. 422).

945. The asserted claims of the '536 Patent claim a method of treating psoriasis, which comprises orally administering to a patient having psoriasis, stereomerically pure apremilast. JSF ¶¶ 40–41 (ECF No. 422).

946. The asserted claims of the '638 and '536 Patents gave Otezla its safety profile, its efficacy, its oral route of administration, and its unique PDE4-inhibiting mechanism of action, which in turn made Otezla a clinical success. Trial Tr. at 311:2–22 (Alexis Direct 6.15.21).

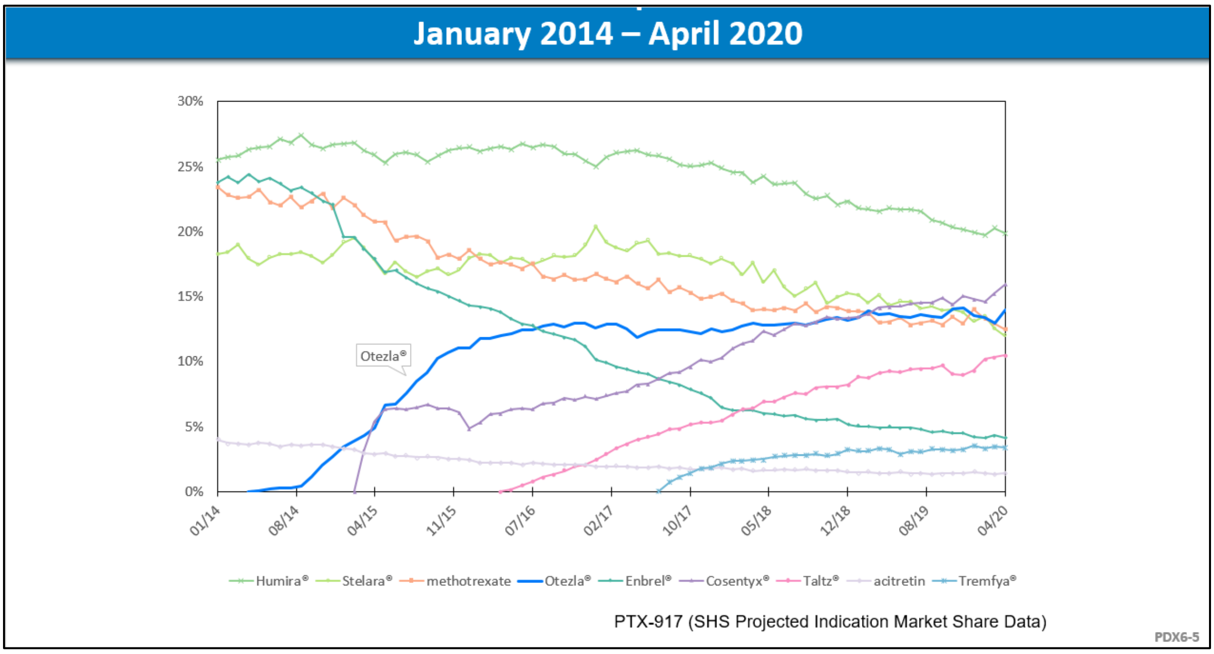
g) Otezla is a commercial success.

(1) Otezla achieved marketplace success.

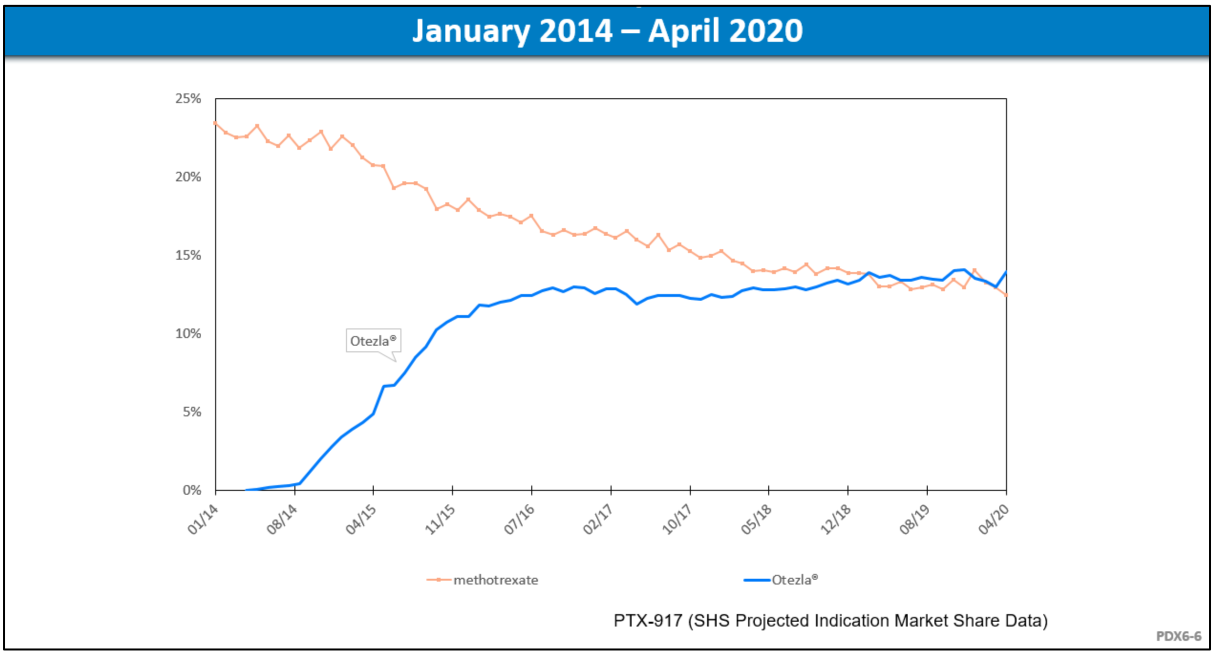
947. At trial, Amgen's economic expert, Dr. Chris Vellturo, testified without rebuttal or contradiction that Otezla achieved marketplace success. Trial Tr. at 349:18–350:21 (Vellturo Direct 6.15.21) (referencing PDX6-2); 1042:13–24 (Hofmann Cross 6.22.21).

948. After Otezla's launch in 2014, it rapidly gained a significant share of the highly competitive market for systemic psoriasis patients and has maintained and even expanded that share despite five new biologic treatments for psoriasis from major pharmaceutical companies entering the market, Cosentyx from Novartis, Taltz from Eli Lilly, Tremfya from Johnson and

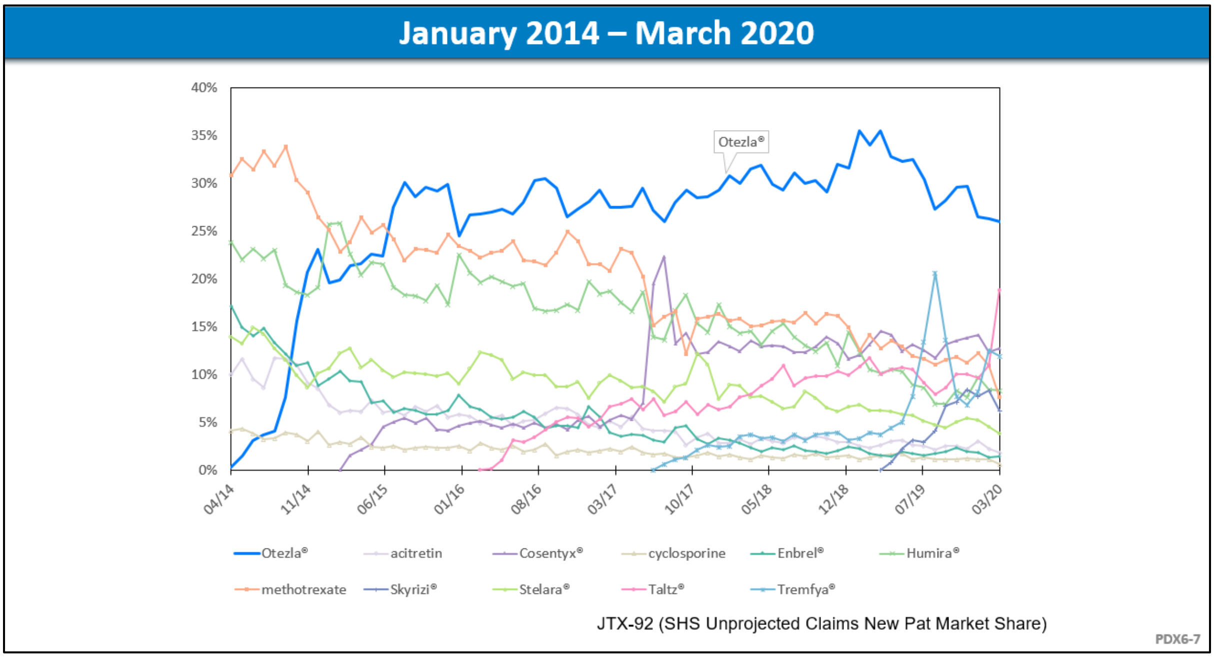
Johnson, Ilumya from Merck, and Skyrizi from AbbVie. Trial Tr. at 349:25–350:9, 354:13–355:1, 356:23–357:3 (Vellturo Direct 6.15.21); PTX-917; PDX6-5.



949. Otezla prescription share among systemic psoriasis treatments surpassed methotrexate in 2019, despite the fact that methotrexate is available in generic from a wide set of suppliers, and as a result has significant cost and insurance advantages over branded products like Otezla. Trial Tr. at 350:10–15 (Vellturo Direct 6.15.21); PTX-917; PDX6-6.



950. Within a year of its approval for psoriasis Otezla had the highest share of prescriptions for systemic treatments among treatment-naïve patients for psoriasis, i.e. patients who are either initiating systemic therapy for the first time or who are restarting therapy after an extended absence. Trial Tr. at 350:16–21, 356:10–15 (Vellturo Direct 6.15.21); PTX-917; PDX6-7.



951. Treatment naïve systemic therapy prescriptions evidences how prescribers are treating patients that are coming into the market, and filters out shares attributable to patients that are already established on a particular therapy. Trial Tr. at 356:16–21 (Vellturo Direct 6.15.21).

952. Roughly 1.7 million prescriptions were written for Otezla between Otezla's 2014 launch and April 2020. Trial Tr. at 353:22–354:1 (Vellturo Direct 6.15.21); PTX-917.

(2) Nexus: key attributes and physician surveys

953. The key attributes of Otezla (namely Otezla's PDE4-inhibiting mechanism of action, its superior safety profile, its efficacy, and the absence of barriers to patient adherence), drove demand for Otezla, and that demand for Otezla would have been dramatically different

if not for the patented inventions of the ’638 and ’536 Patents, which allowed Otezla to have those features. Trial Tr. at 358:13–359:1, 377:13–378:6 (Vellturo Direct 6.15.21).

954. Surveys of prescribers show that Otezla’s safety profile, efficacy, route of administration, ease of continued use, and lack of required lab monitoring, were all major drivers of physicians’ demand for Otezla use. Trial Tr. at 359:15–21, 362:6–13 (Vellturo Direct 6.15.21); JTX-194 at JTX-194_8; JTX-196 at JTX-196_26.

955. In a 2015 survey, dermatologists chose Otezla’s overall safety, ease of patient administration, lack of lab monitoring, and mechanism of action as its top-rated attributes. Trial Tr. at 360:13–361:12 (Vellturo Direct); JTX-194 at JTX-194_8.

956. In a 2017 survey of dermatologists, prescribers rated Otezla higher than all other products on long-term safety, and rated Otezla significantly higher than methotrexate. Otezla. JTX-195 at JTX-195_23. The dermatologists also rated Otezla significantly higher than methotrexate and all biologic treatments in lab-monitoring requirements, route of administration, and pre-screening requirements in that survey. Otezla. JTX-195 at JTX-195_24. The top reasons dermatologists gave in the survey when asked why they prescribed Otezla were its lack of lab monitoring requirements and its long-term safety. JTX-195 at JTX-195_28.

957. In a 2019 survey of dermatologists, 70% of dermatologists rated Otezla highly in offering excellent long-term safety, compared to just 7% for methotrexate. JTX-196 at JTX-196_32. In the same survey, dermatologists identified lack of lab monitoring, favorable safety profile, and convenient route of administration as the top reasons they prescribe Otezla. Trial Tr. at 361:18–362:3 (Vellturo Direct 6.15.21); JTX-196 at JTX-196_26. Moreover, Otezla significantly outperformed both methotrexate and prescription topical treatments in promoting high patient compliance. JTX-196 at JTX-196_39.

958. Across multiple surveys of dermatologists in 2018 and 2019 Otezla outperformed both methotrexate and prescription topical treatments in offering long term safety and ease of monitoring, and Otezla performed on par with methotrexate in short-term tolerability. JTX-196 at JTX-196_35.

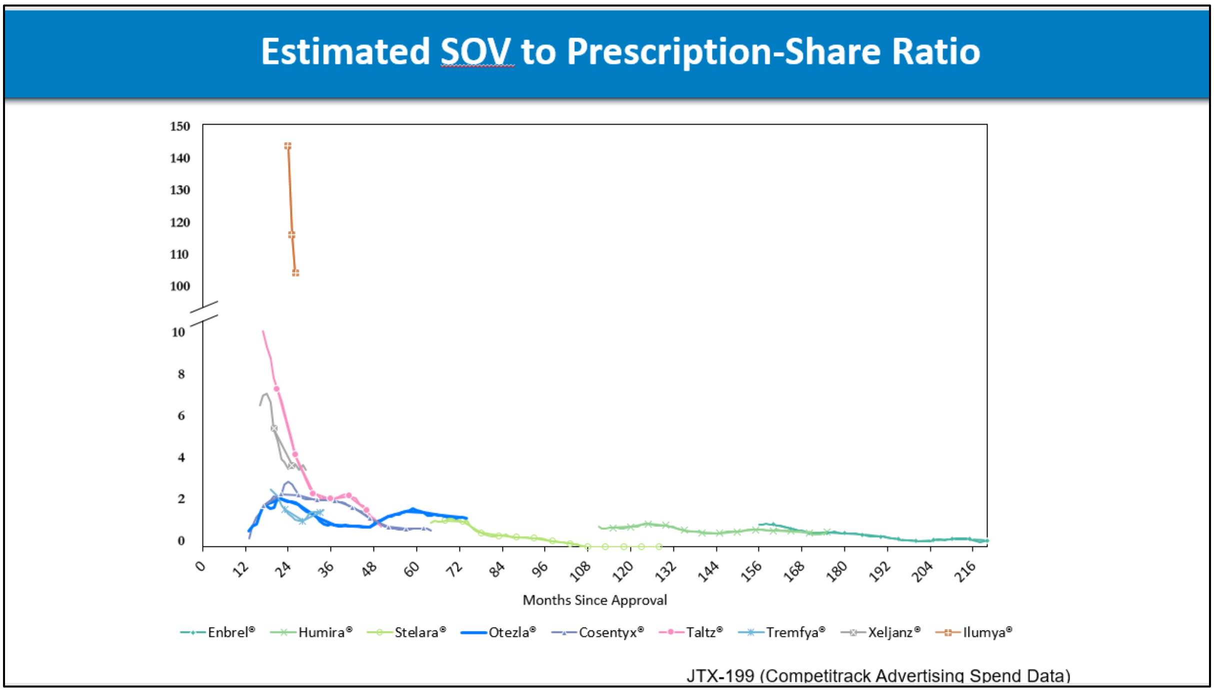
(3) Nexus: advertising

(a) Share-of-voice analysis

959. Otezla's advertising and pricing were comparable to that of competitors, and did not disproportionately contribute to Otezla's commercial success. Trial Tr. at 371:11–20 (Vellturo Direct 6.15.21).

960. A share-of-voice analysis is an economic measure of how much a given product's market performance appears to rely on advertising—it is essentially the ratio of a product's share of all advertising expenditures for a drugs for a specific disease to the product's share of all prescriptions written for that disease. Trial Tr. at 365:23–366:14 (Vellturo Direct 6.15.21). Larger ratios indicate that a product's market performance is reliant on advertising whereas smaller ratios indicate market performance is not being propped up by advertising spend. Trial Tr. at 366:8–14 (Vellturo Direct 6.15.21). When performing a share of voice analysis it is important to control for the time each product being analyzed has been on the market, as most branded products have relatively high marketing expenditures and relatively low prescription shares shortly after launch, and over time the advertising typically declines and prescription shares increase. Trial Tr. at 366:15–24 (Vellturo Direct 6.15.21).

961. Otezla's ratio was smaller than Taltz and Cosentyx, comparable to Tremfya, and dramatically smaller than Ilumya. Trial Tr. at 367:3–367:24 (Vellturo Direct 6.15.21); PDX6-14; JTX-199.



962. One of the documents Mr. Hofmann relied on in testifying about Otezla's advertising indicates that Humira and Enbrel spent more on TV advertising than Otezla in 2015; Humira, Enbrel and Cosenytx outspent Otezla in 2016; Humira, Cosenytx and Taltz outspent Otezla in 2017; and Humira and Cosentyx outspent Otezla in 2018. DDX-6.11; JTX-82 at JTX-82_84.

963. Mr. Hofmann did not do any share-of-voice analysis to analyze Otezla's marketing expenditures compared to those of other psoriasis treatments and, therefore, could not say that marketing for Otezla was in any way excessive. Trial Tr. at 1056:12–1057:12 (Hofmann Cross 6.22.21).

(b) Messages emphasized in Otezla materials

964. Otezla marketing materials consistently emphasized the key attributes of Otezla made possible by the inventions claimed in the '638 and '536 Patents. Trial Tr. at 363:5–16, 364:23–365:4 (Vellturo Direct 6.15.21); 1043:14–19, 1054:11–1055:5 (Hofmann Cross 6.22.21); *see e.g.*, PTX-970 at PTX-970_2 (emphasizing Otezla's efficacy, lack of required lab monitoring, and PDE-4 mechanism of action).

965. The digital sales materials that sales representatives used when informing health care professionals contained slides that emphasized Otezla's PDE4 mechanism of action, efficacy, side effect profile, and lack of lab monitoring requirements for. Trial Tr. at 363:22–364:6 (Vellturo Direct 6.21.21); JTX-198 at JTX-198_2–4 (PDE4 inhibiting mechanism of action), JTX-198_5–54 (efficacy), JTX-198_55–68 (side effect profile); PTX-970 at PTX-970_2 (lack of lab monitoring requirements).

966. Otezla's consumer consumer-facing website emphasized its oral administration, efficacy, and unique mechanism of action. Trial Tr. at 364:10–20 (Vellturo Direct 6.15.21); PTX-1293 at PTX-1293_1.

(4) Nexus: insurance pricing and coverage

967. An insurance formulary is a list of drugs that an insurance company covers. Trial Tr. at 369:13–21 (Vellturo Direct 6.15.21).

968. Some insurance company formularies require a doctor to first prescribe other preferred drugs before insurance will cover the drug in question—this is called a "step edit." Trial Tr. at 370:7–17 (Vellturo Direct 6.15.21).

969. If a drug is on fewer formularies than competitors, is subject to more step edits than its competitors, or otherwise has less favorable formulary coverage than competitors, that can be a key barrier to a drug's commercial success. Trial Tr. at 369:14–370:1 (Vellturo Direct 6.15.21).

970. Many formularies had step edits in place for Otezla, and would only cover Otezla after a doctor first prescribed a preferred drug like Humira. Trial Tr. at 370:7–17 (Vellturo Direct 6.15.21).

971. Physician survey results indicate that unfavorable formulary positioning relative to established biologics and methotrexate, and high out-of-pocket costs to patients, were among

the primary reasons physicians gave for not prescribing Otezla. Trial Tr. at 369:5–370:6 (Vellturo Direct 6.15.21); JTX-195 at JTX-195_29; JTX-194 at JTX-194_37.

972. In a 2017 survey of dermatologists, prescribers reported that issues with formulary coverage and out-of-pocket costs were the two primary reasons they did not prescribe Otezla. JTX-195 at JTX-195_29.

973. In a 2019 survey of dermatologists, prescribers reported that lack of insurance coverage was the primary reason they did not prescribe Otezla. JTX-196 at JTX-196_30.

974. Celgene and Amgen, like almost all branded drugs for the treatment of psoriasis, worked to attain a more competitive formulary position for Otezla by offering discounts to insurers to level the playing field. Trial Tr. at 370:7–370:17 (Vellturo Direct 6.15.21); 1053:1–9 (Hofmann Cross 6.22.21).

975. Even with the discounts provided, Otezla's wholesale acquisition cost, the cost that distributors pay to acquire Otezla has increased since launch. Trial Tr. 1053:12–21 (Hofmann Cross 6.22.21); JTX-82 at JTX-82_24.

976. In order to overcome barriers posed by high out-of-pocket costs to patients, Celgene and Amgen, like almost all branded drugs including Humira, launched a co-pay program that helped some patients get reimbursed for co-pays. Trial Tr. at 370:18–371:10 (Vellturo Direct 6.15.21). Such programs are standard operating practice among branded psoriasis and psoriatic arthritis medications and Dr. Hofmann agreed that he does not know whether Otezla's programs were more utilized than the programs for other psoriasis treatments. Trial Tr. at 371:3–371:10 (Vellturo Direct 6.15.21); 1048:22–1049:2, 1050:6–10 (Hofmann Cross 6.22.21).

(5) Nexus: samples

977. The availability of samples of Otezla did not materially impact Otezla's success in the marketplace because samples of Otezla do not affect a dermatologist's upstream

prescribing decisions. Trial Tr. at 312:20–313:18 (Alexis Direct 6.15.21); 933:9–12 (Gilmore Cross 6.21.21) (testifying that she bases prescribing decisions on her best medical judgments and the patients desires and therapeutic goals); 1043:24–1044:1 (Hofmann Cross 6.22.21) (agreeing that prescribing decisions are based on a drug's merits). In fact, Dr. Gilmore testified that following the titration that is in the Otezla sample packs encourages patients to ***stop*** taking Otezla. Trial Tr. at 929:8–13 (Gilmore 6.22.21).

978. Physicians make prescribing decisions based on which medicine will be safe, effective, and appropriate for the patient, not whether they have samples on hand for a particular drug. Trial Tr. at 312:20–313:18 (Alexis Direct 6.15.21); 933:9–12 (Gilmore Cross 6.21.21) (testifying that she bases prescribing decisions on her best medical judgments and the patients desires and therapeutic goals); 1043:24–1044:1 (Hofmann Cross 6.22.21) (agreeing that prescribing decisions are based on a drug's merits).

979. Otezla sample packs are unique among samples for all psoriasis and psoriatic arthritis treatments, because they come in starter packs that show the patient how to adhere to the titration schedule. Trial Tr. at 908:18-909:15, 928:3–25 (Gilmore Cross 6.21.21); 1050:11–1051:12 (Hofmann Cross 6.22.21).

980. The studies that Dr. Gilmore relied upon are not specific to Otezla. Trial Tr. at 927:13–929:7 (Gilmore Cross 6.21.21).

(6) Nexus: blocking patent

981. The '358 Patent did not become public knowledge until it issued on February 1, 2000. Trial Tr. at 373:13–22 (Vellturo Direct 6.15.21).

982. The '358 Patent could not have acted as a so-called "blocking patent" by dampening economic incentives to develop the inventions of the '638 Patent, because the inventions of the '638 Patent were conceived by October 21, 1999, and reduced to practice by

December 1999, before the existence of the ’358 Patent became known. Trial Tr. at 374:1–13 (Vellturo Direct 6.15.21).

983. The ’358 Patent could not have dampened economic incentives to develop the inventions of the ’536 Patent before the existence of the ’358 Patent became known on February 1, 2000. Trial Tr. at 374:18–25 (Vellturo Direct 6.15.21).

984. For an earlier patent to serve as a blocking patent, others need to perceive that they could not obtain rights to the alleged blocking patent. Trial Tr. at 375:12–17 (Vellturo Direct 6.15.21).

985. Other than Celgene, no other companies were trying to develop thalidomide analogs as PDE4 inhibitors in the late 1990s. Trial Tr. at 131:25–132:4 (Schafer Direct 6.14.21); 1328:18–22 (Davies Direct 6.23.21).

986. Starting in 1999, and continuing through 2004, Celgene began engaging with other pharmaceutical companies in the hopes that those companies would take a license to Celgene’s SelCID technology, including the ’358 Patent, and apremilast specifically to develop apremilast as a drug. Trial Tr. at 156:22–157:10, 165:6–9 (Schafer Direct 6.14.21); 376:12–15 (Vellturo Direct 6.15.21).

987. In the period Celgene was attempting to license its SelCID technology it was a small company and did not have the financial or human capital to pursue the long and expensive process of developing a drug on its own. Trial Tr. at 164:23–165:5, 164:14–21 (Schafer Direct 6.14.21); 397:19–398:11 (Vellturo Cross 6.15.21).

988. If one of the pharmaceutical companies Celgene approached had chosen to license apremilast they could have developed it for the treatment of inflammatory diseases, including by making pharmaceutical formulations containing apremilast and developing methods of treatment using apremilast. Trial Tr. at 167:21–168:10 (Schafer Direct 6.14.21).

989. GSK, one of the companies that Celgene approached about licensing apremilast ultimately decided not to license apremilast because of the compound's structural similarities to thalidomide. Trial Tr. at 231:18–232:9 (Knowles Direct 6.15.21)

990. The companies Celgene approached about licensing apremilast included GlaxoSmithKline, Wyeth, Eli Lilly, Roche, Forest Laboratories, Aventis, Bristol Myers Squibb, Daiichi-Sankyo, Pharmacia, Boehringer Ingelheim, and Amgen. Tr. at 166:25–167:3, 167:13–18 (Schafer Direct 6.14.21); JTX-210 at JTX-210_44.

991. Celgene's unsuccessful attempts to out-license apremilast indicates that the '358 Patent did not act as a blocking patent during the relevant timeframe, because other companies that wanted to pursue opportunities related to apremilast could have accessed Celgene's intellectual property via the licensing program. Trial Tr. at 376:19–377:6 (Vellturo Direct 6.15.21).

992. Mr. Hofmann testified that he does not know why no agreement to license apremilast and Celgene's other SelCID technology was reached in the early 2000s. Trial Tr. 1062:4–8 (Hofmann Cross 6.22.21).

h) Industry acquiescence

993. At least seventeen generic drug manufacturers have acknowledged that certain of the patents-in-suit are valid and enforceable or otherwise acquiesced in their validity and enforceability, which confirms that the industry has acquiesced to the validity of these patents.

994. Alkem has admitted, for itself and its Affiliates, that the '638 and the '536 Patents are valid and enforceable. Civ. No. 3:18-11265, ECF No. 70 (Stipulation and Order).

995. Amneal has admitted, for itself and its Affiliates, that the '638 and the '536 Patents are valid and enforceable. Civ. No. 3:18-11358, ECF No. 42 (Stipulation and Order).

996. Annora has admitted, for itself and its Affiliates, that the '638 and the '536 Patents are valid and enforceable. Civ. No. 3:18-11220, ECF No. 49 (Stipulation and Order).

997. Aurobindo has admitted, for itself and its Affiliates, that the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-11219, ECF No. 43 (Stipulation and Order).

998. Cipla has admitted, for itself and its Affiliates, that the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-11262, ECF No. 38 (Stipulation and Order).

999. DRL has admitted, for itself and its Affiliates, that the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-11269, ECF No. 58 (Stipulation and Order).

1000. Emcure has admitted, for itself and its Affiliates, that the ’638 Patent is valid and enforceable. Civ. No. 3:18-11218, ECF No. 44 (Stipulation and Order).

1001. Glenmark has agreed, not to infringe the ’638 or ’536 Patents. Civ. No. 3:18-11158, ECF No. 39 (Stipulation and Order).

1002. Macleods has admitted, for itself and its Affiliates, that the ’638 Patent is valid and enforceable. Civ. No. 3:18-11212, ECF No. 37 (Stipulation and Order).

1003. Mankind has admitted, for itself and its Affiliates, that the ’638 Patent is valid and enforceable. Civ. No. 3:18-11081, ECF No. 50 (Stipulation and Order).

1004. MSN has admitted, for itself and its Affiliates, that the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-11213, ECF No. 40 (Stipulation and Order).

1005. Pharmascience has admitted, for itself and its Affiliates, that with respect to the Pharmascience ANDA and ANDA Product, that the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-11545, ECF No. 63 (Stipulation and Order).

1006. Prinston has admitted, for itself and its Affiliates, that the ’638 Patent is valid and enforceable. Civ. No. 3:18-11216, ECF No. 51 (Stipulation and Order).

1007. Shilpa has admitted, for itself and its Affiliates, that the ’638 Patent is valid and enforceable. Civ. No. 3:18-11157, ECF No. 43 (Stipulation and Order).

1008. Teva has admitted, for itself and its Affiliates, that with respect to the Teva ANDA the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-11215, ECF No. 71 (Stipulation and Order).

1009. Torrent has admitted, for itself and its Affiliates, that the ’638 Patent is valid and enforceable. Civ. No. 3:18-11156, ECF No. 63 (Stipulation and Order).

1010. Unichem has admitted, for itself and its Affiliates, that the ’638 and the ’536 Patents are valid and enforceable. Civ. No. 3:18-cv-11268, ECF No. 41 (Stipulation and Order).

E. Defendants Have Failed to Prove that the ’638 Composition Patent is Invalid for Obviousness-Type Double Patenting.

1011. Defendants’ ODP challenge to Claims 3 and 6 of the ’638 Patent is based solely on Claim 31 of the ’283 Patent. Joint Final Pretrial Order at 111 ¶ 15 (ECF No. 422).

1. The difference in expiration dates between the ’638 and ’283 Patents is solely attributable to statutorily authorized time extensions.

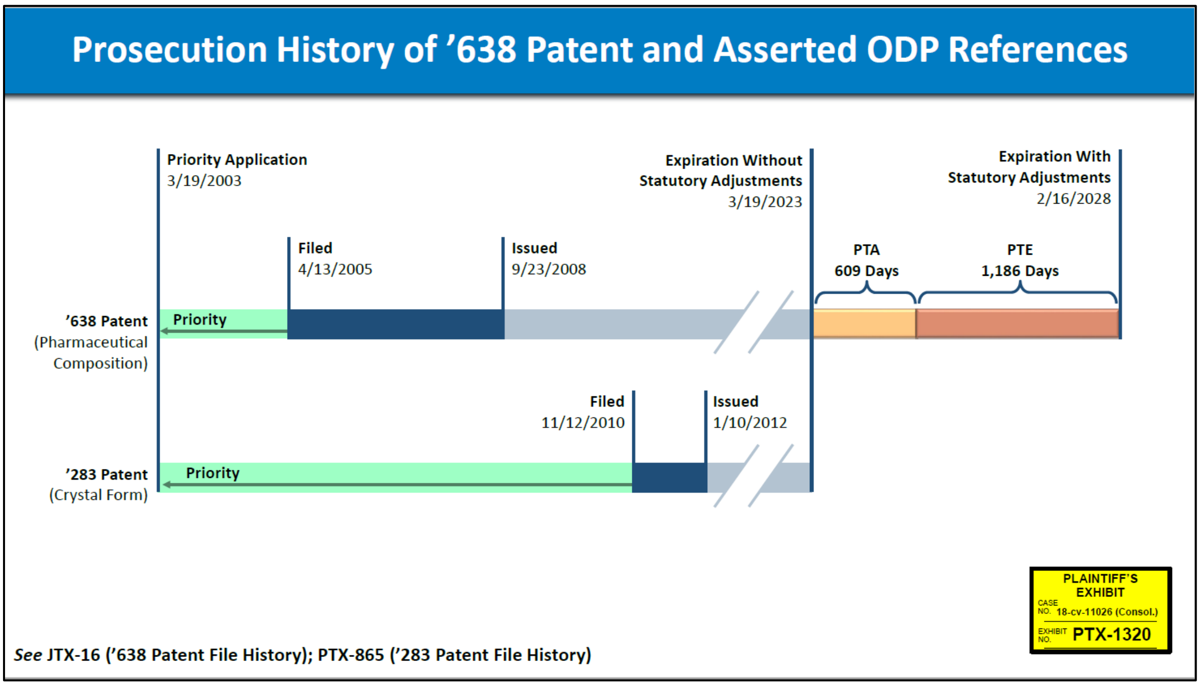
1012. The application for the ’638 Patent was filed on April 13, 2005. Trial Tr. at 1553:10–21, 1562:17–25 (Smith Direct 6.24.21); PTX-1320. The ’638 Patent issued on September 23, 2008, and it will expire on February 16, 2028. *Id.* The ’638 Patent claims priority to the application for U.S. Patent No. 6,962,940 (“the ’940 Patent”), which was filed on March 19, 2003. *Id.*

1013. The application for the ’283 Patent was filed on November 12, 2010. Trial Tr. at 1563:4–9 (Smith Direct 6.24.21); PTX-1320. The ’283 Patent issued on January 10, 2012, and it will expire on March 19, 2023. *Id.* The ’283 Patent claims priority to the application for the ’940 Patent, which was filed on March 19, 2003. *Id.*

1014. The ’638 Patent expires later than the ’283 Patent solely because the ’638 Patent received two statutorily authorized time extensions: a patent-term adjustment (“PTA”) of 609 days and a patent-term extension (“PTE”) of 1,186 days. Trial Tr. at 1552:13–18, 1553:14–21,

1555:3–10, 1558:21–1559:4, 1563:10–18 (Smith Direct 6.24.21); PTX-1318; PTX-1319; PTX-1320.

1015. The key events in the file histories of the ’638 and ’283 Patents are reflected in the timeline below, PTX-1320:



1016. Defendants’ ODP challenge focuses solely on the PTA that the ’638 Patent received. Joint Final Pretrial Order, Ex. D ¶¶ 348–54 (ECF No. 422).

1017. PTA and PTE are statutorily authorized time extensions that restore patent term that would otherwise be lost to delays arising from periods of government review. Trial Tr. at 1539:9–1541:3 (Smith Direct 6.24.21).

1018. PTA restores days of patent term lost to pre-issuance delays by the Patent Office in the examination process. Trial Tr. at 1539:19–1540:13 (Smith Direct 6.24.21).

1019. Because the term of a patent issuing from an application that was filed after June of 1995 (a “post-GATT” patent) begins to run on the filing date of the earliest application to which the patent claims priority, each day of delay by the Patent Office in examining the application effectively reduces the term of the patent by one day. Trial Tr. 1537:16–1538:19, 1539:19–1540:13 (Smith Direct 6.24.21).

1020. PTE restores days of patent term lost to post-issuance delays arising from review of a patented product by a regulatory agency, such as the FDA. Trial Tr. at 1540:14–1541:3 (Smith Direct 6.24.21).

1021. If a patent covers a product that is regulated by a federal agency and the agency's review of the product has not concluded by the time the patent issues, the patent owner effectively loses days of term until the review concludes—during that time, the patent owner has a patent in hand but cannot offer the product it covers to the public. Trial Tr. at 1540:14–1541:3, 1557:10–20, 1558:3–11 (Smith Direct 6.24.21).

1022. In the event of either type of delay (by the PTO or a regulatory agency), the patent is awarded additional days of term, in the form of PTA or PTE. Trial Tr. at 1539:9–1541:3 (Smith Direct 6.24.21).

1023. The amount of additional term awarded in the form of PTA or PTE is based on the amount of delay and is calculated pursuant to formulas provided by statute, as implemented by the applicable Patent Office policies, practices, and procedures. Trial Tr. at 1539:9–1541:3, 1544:8–12, 1557:5–9 (Smith Direct 6.24.21); PTX-1318; PTX-1319.

1024. It is undisputed that the two statutorily authorized time extensions that the '638 Patent received were properly calculated and awarded pursuant to the applicable Patent Office policies, practices, and procedures. Trial Tr. at 1555:3–10, 1558:21–1559:4 (Smith Direct 6.24.21); PTX-1318; PTX-1319.

1025. The '638 Patent was entitled to, and received, 609 days of PTA. Trial Tr. at 1555:3–10 (Smith Direct 6.24.21); PTX-1318.

1026. The Patent Office missed two applicable statutory deadlines during its examination of the application for the '638 Patent: it issued a first office action 461 days after the 14-month deadline, and it concluded prosecution 163 days after the 3-year deadline. Trial Tr. at 1553:22–1554:11 (Smith Direct 6.24.21).

1027. There were also 15 days of applicant delay because Celgene was granted a single 30-day extension of time and used 15 days of it. Trial Tr. at 1554:12–22 (Smith Direct).

1028. The total PTA to which a patent is entitled is equal to the sum of Patent Office delay, minus any applicant delay, which is 609 days in total for the ’638 Patent. Trial Tr. at 1554:23–1555:10 (Smith Direct 6.24.21); PTX-1318.

1029. Celgene did not file a terminal disclaimer in connection with the ’638 Patent, tying its expiration to the expiration of the ’283 Patent, nor did it file a terminal disclaimer in connection with the ’283 Patent, tying its expiration to the expiration of the ’638 Patent. Trial Tr. at 1561:20–1562:2 (Smith Direct 6.24.21).

1030. The ’638 Patent also received, and was entitled to, 1,186 days of PTE. Trial Tr. at 1558:21–1559:4 (Smith Direct 6.24.21); PTX-1319.

1031. There were 1,640 days in the “post-grant testing phase” and 366 days in the “approval phase.” Trial Tr. at 1557:10–1558:15 (Smith Direct 6.24.21); PTX-1319.

1032. The total PTE to which the ’638 Patent was entitled is equal to the sum of half of the days in the post-grant testing phase and all of the days in the approval phase. Trial Tr. at 1556:6–1558:15 (Smith Direct 6.24.21); PTX-1319.

1033. The ’638 Patent was awarded a PTE of 1,186 days. Trial Tr. at 1558:21–1559:4 (Smith Direct 6.24.21); PTX-1319.

1034. But for the two statutorily authorized time extensions it received—a PTA of 609 days and a PTE of 1,186 days—the ’638 Patent would expire on the same day as the ’283 Patent: March 19, 2023. Trial Tr. at 1552:13–18, 1553:14–21, 1555:3–10, 1558:21–1559:4, 1563:10–18 (Smith Direct 6.24.21); PTX-1318; PTX-1319; PTX-1320.

1035. The ’283 Patent is not a proper double-patenting reference for the ’638 Patent because the difference in expiration dates between the ’638 Patent and the ’283 Patent is solely attributable to two statutorily authorized time extensions.

2. The difference in expiration dates between the ’638 and ’283 Patents is not the result of any prosecution gamesmanship.

1036. It would be inequitable to apply double patenting in the particular circumstances of this case because the difference in expiration dates between the ’638 and ’283 Patents is not the result of any prosecution gamesmanship. Trial Tr. at 1552:13–18, 1564:1–17, 1568:6–10 (Smith Direct 6.24.21).

1037. Defendants do not contend that the difference in expiration dates between the ’638 and ’283 Patents is the result of prosecution gamesmanship and have not offered any evidence of such gamesmanship. Trial Tr. at 1564:18–24 (Smith Direct 6.24.21).

1038. One specific form of prosecution gamesmanship that may result in a difference in expiration dates between two patents is “strategic delay,” which refers to taking actions to intentionally delay the issuance of a patent. Trial Tr. at 1546:18–1547:11 (Smith Direct 6.24.21).

1039. For a pre-GATT patent, which expires 17 years from the date of issuance, delaying issuance can delay expiration, potentially resulting in a difference in expiration dates between two related patents. Trial Tr. at 1546:18–1547:11 (Smith Direct 6.24.21).

1040. The difference in expiration dates between the ’638 and ’283 Patents is not the result of strategic delay. Trial Tr. at 1564:2–6 (Smith Direct 6.24.21).

1041. The ’638 Patent is a post-GATT patent, so its expiration date is not tied to its issue date. Trial Tr. at 1553:14–21 (Smith Direct 6.24.21).

1042. Celgene did not intentionally delay the issuance of the ’638 Patent to extend the patent’s term. Trial Tr. at 1564:2–6 (Smith Direct 6.24.21). Celgene was granted a single 30-day extension of time, of which it used just 15 days, and those days were ultimately subtracted from the PTA that the ’638 Patent was awarded. Trial Tr. at 1554:12–22 (Smith Direct 6.24.21).

1043. Another specific form of prosecution gamesmanship that may result in a difference in expiration dates between two patents is “structuring priority claims,” which refers

to intentionally declining to make a claim of priority in order to obtain a later expiration date. Trial Tr. at 1546:18–25, 1547:12–1549:11 (Smith Direct 6.24.21).

1044. For a post-GATT patent, which expires 20 years after the filing date of the earliest application to which it claims priority, declining to make a claim of priority to an earlier application—when such a claim could have been made—can delay expiration, potentially resulting in a difference in expiration dates between two related patents. Trial Tr. at 1547:12–1549:11 (Smith Direct 6.24.21).

1045. The difference in expiration dates between the ’638 and ’283 Patents is not the result of structuring priority claims. Trial Tr. at 1564:7–13 (Smith Direct 6.24.21).

1046. The ’638 and ’283 Patents each claim priority to a common prior application, so—but for any statutory extensions—they would expire on the same date. Trial Tr. at 1564:7–13 (Smith Direct 6.24.21); PTX-1320.

1047. More broadly, the difference in expiration dates between the ’638 and ’283 Patents is not the result of any form of prosecution gamesmanship or any improper conduct by Celgene. Trial Tr. at 1552:13–18, 1564:1–17, 1568:6–10 (Smith Direct 6.24.21).

1048. Defendants did not present testimony from an expert in Patent Office policies, practices, or procedures, or otherwise offer any evidence that the difference in expiration dates between the ’638 and ’283 Patents is the product of prosecution gamesmanship or improper conduct by Celgene.

1049. Additional considerations show that it would be particularly inequitable to apply double patenting in the circumstances of this case.

1050. But for the Patent Office’s delays, much of the ’638 Patent’s challenged PTA would instead be unchallenged PTE. Trial Tr. at 1565:1–6, 1567:12–1568:5 (Smith Direct 6.24.21).

1051. Because PTA arises from the period *before* a patent issues and PTE arises from the period *after* a patent issues (but before regulatory approval), there may effectively be a "tradeoff" between PTA and PTE, such that more delay by the Patent Office results in a patent being entitled to less PTE but more PTA, and vice versa. Trial Tr. at 1565:7–1567:9 (Smith Direct 6.24.21).

1052. In the circumstances of this case, if the Patent Office had not delayed issuance of the '638 Patent, the '638 Patent would have received much of the same statutory extension, but in the form of PTE rather than PTA. Trial Tr. at 1565:1–6, 1567:12–1568:5 (Smith Direct 6.24.21).

1053. It would be inequitable to cut short the term of the '638 Patent by applying double patenting based on the form of statutory extension the '638 Patent received, solely as a result of Patent Office delays and not any gamesmanship by Celgene.

1054. Additionally, the '283 Patent is a separately patentable improvement that Celgene pursued years after the '638 Patent issued. Trial Tr. at 1559:5–1561:16, 1562:10–1563:10 (Smith Direct 6.24.21); PTX-1320.

1055. The examiner of the application for the '283 Patent determined that the invention claimed by the '283 Patent (crystal forms of stereomerically pure apremilast) is patently distinct from the basic invention claimed by the '638 Patent (stereomerically pure apremilast). Trial Tr. 1559:5–1561:16 (Smith Direct 6.24.21).

1056. Defendants offered no evidence to the contrary that the '283 Patent is separately patentable over the '638 Patent—Dr. Gribble's testimony did not address this question at all. Trial Tr. at 647:1–10 (Gribble Cross 6.18.21).

1057. It would be inequitable for the '283 Patent to cut short the term of patent protection over the basic invention claimed by the '638 Patent, solely because of delays to the

prosecution of the ’638 Patent that were outside Celgene’s control and not the product of any gamesmanship by Celgene.

3. Defendants have failed to carry their burden on patentable distinctness.

1058. Defendants have failed to carry their burden to adduce clear and convincing evidence to show that the basic invention claimed by Claims 3 and 6 of the ’638 Patent (stereomerically pure apremilast) is patentably indistinct from the improvement claimed by Claim 31 of the ’283 Patent (crystal forms of stereomerically pure apremilast).

1059. Defendants’ only evidence is the testimony of Dr. Gribble. However, rather than considering the subject matter of the claims as a whole, Dr. Gribble focused on picking out particular elements of the claims in each patent. Trial Tr. at 648:13-649:15 (Gribble Cross 6.18.21).

1060. Dr. Gribble acknowledged that he had testified that apremilast and a particular crystalline form of apremilast are “different inventions” that “involve different skills and different expertise.” Trial Tr. at 648:1–648:11 (Gribble Cross 6.18.21).

1061. Dr. Gribble’s testimony regarding the ’638 and ’283 Patents did not mention patentable distinctness. Trial Tr. at 615:20–616:16 (Gribble Direct 6.18.21).

1062. Neither Dr. Gribble nor any other witness testified that the inventions claimed in Claims 3 and 6 of the ’638 Patent are patentably indistinct from, or obvious over, Claim 31 of the ’283 Patent.

X. THE ’536 PSORIASIS PATENT ASSERTED CLAIM IS INFRINGED

1063. Both Sandoz and Zydus have stipulated to infringement of the ’638 Patent. *See* SSF (A3) ¶ 9–10 (ECF No. 422); Civ. No. 18-11026, ECF No. 246; ZSF (A2) ¶ 14–15 (ECF No. 422); Civ. No. 18-11267, ECF No. 54.

A. Sandoz's Proposed ANDA Product Infringes the '536 Psoriasis Patent.

1064. The submission of Sandoz's ANDA to the FDA seeking approval for Sandoz's ANDA is an act of infringement with respect to claim 6 of the '536 Patent under 35 U.S.C. § 271(e)(2)(A), if this claim is not found to be invalid or unenforceable. *See* SSF (A3) ¶ 9 (ECF No. 422); Civ. No. 18-11026, ECF No. 246.

1065. Upon final approval of Sandoz's ANDA, the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Sandoz's ANDA Products will infringe claim 6 of the '536 Patent under 35 U.S.C. § 271(a), (b) and/or (c), if this claim is not found to be invalid or unenforceable. *See* SSF (A3) ¶ 10 (ECF No. 422); Civ. No. 18-11026, ECF No. 246.

B. Zydus's Proposed ANDA Product Infringes the '536 Psoriasis Patent.

1066. The submission of Zydus's ANDA to the FDA seeking approval for Zydus's ANDA Products is an act of infringement with respect to claim 6 of the '536 Patent under 35 U.S.C. § 271(e)(2)(A), if this claim is not found to be invalid or unenforceable. *See* ZSF (A2) ¶ 14; Civ. No. 18-11267, ECF No. 54.

1067. Upon final approval of Zydus's ANDA, the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Zydus's ANDA Products will infringe claim 6 of the '536 Patent under 35 U.S.C. § 271(a), (b) and/or (c), if this claim is not found to be invalid or unenforceable. *See* ZSF (A2) ¶ 15 (ECF No. 422); Civ. No. 18-11267, ECF No. 54.

XI. THE '536 PSORIASIS PATENT ASSERTED CLAIM IS NOT INVALID

A. Person of Ordinary Skill in the Art for the '536 Psoriasis Patent

1068. The POSA would have at least a bachelor's degree in a field such as pharmaceutical chemistry, chemistry, pharmaceutics, or some related discipline. They would have about three to five years of work experience in the area or comparable level of education and training such as Ph.D. with one to two years' experience in the area. And they would have

worked on a team having access to other team members with experience in designing, evaluating, and administering pharmaceutical formulations obtained by some combination of education with work experience, such as a physician with knowledge and experience relevant to any methods of treatment to which the patients are directed, if applicable. Trial Tr. at 1300:23–1301:11 (Davies Direct 6.23.21); Trial Tr. at 200:9–22 (Knowles Direct 6.15.21).

1069. Regardless of the definition of a POSA used, Dr. Davies's opinions do not change. Trial Tr. at 1301:16–18 (Davies Direct 6.23.21).

1070. Regardless of the definition of a POSA used, Dr. Knowles's opinions do not change. Trial Tr. at 1663:10–16 (Knowles Direct 6.25.21).

B. Defendants Have Failed to Prove that the '536 Psoriasis Patent is Invalid for Anticipation.

1071. The asserted claim of the '536 Patent requires stereomerically pure apremilast. JTX-7 at cl. 6.

1072. As discussed above, the '358 Patent does not disclose stereomerically pure apremilast. *See* PF ¶¶ 334–79.

1073. Furthermore, following Example 12 and the general guidance in columns 8 and 9 of the '358 Patent (DTX-174 at 8:63–9:12; 14:34–55) would not always and necessarily produce stereomerically pure apremilast having greater than 98% by weight of the plus isomer. Trial Tr. at 1384:4–13 (Davies Direct 6.23.21).

1074. The Patent Office considered the '358 Patent during the prosecution of the application leading to the '536 Patent. JTX-7 at JTX-7_2.

C. Defendants Have Failed to Prove that the '536 Psoriasis Patent is Invalid for Obviousness.

1. The example compounds of the '358 Patent are not the starting point a POSA would turn to develop a PDE4 inhibitor.

1075. The proposed facts discussed above, PF ¶¶ 539–609, are incorporated herein. The POSA would not have been motivated to select any of the compounds of the '358 Patent

as a starting point for further modification as of March 2002. Trial Tr. at 1302:4–8 (Davies Direct).

2. The POSA would not have been motivated to further modify any of the various identified starting points to arrive at apremilast.

1076. The proposed facts discussed above, PF ¶¶ 610–49, are incorporated herein. The POSA would not have been motivated to further modify any of the variously identified starting points to make apremilast, as of March 2002. Trial Tr. at 1302:4–8 (Davies Direct 6.23.21).

3. The POSA would not have reasonably expected to make apremilast.

1077. The proposed facts discussed above, PF ¶ 650, are incorporated herein. The POSA would not have reasonably expected to be able to make apremilast, as of March 2002. Trial Tr. at 1302:4–8 (Davies Direct 6.23.21).

4. The POSA would not have reasonably expected to obtain the desirable properties of apremilast.

1078. The proposed facts discussed above, PF ¶¶ 651–62, are incorporated herein. The POSA would not have reasonably expected apremilast to have the particular combination of properties it ultimately showed to have, as of March 2002. Trial Tr. at 1302:4–8 (Davies Direct 6.23.21).

5. The combination of the '358 Patent, Dyke 1999, Marriott 2001, Muller 1998 does not render Claim 6 of the '536 Psoriasis Patent obvious.

1079. Asserted claim 6 of the '536 Patent would not have been obvious over the '358 Patent in view of Dyke 1999, Marriott 2001, and Muller 1998 as of March 20, 2002. Trial Tr. at 1700:25–1701:23 (Knowles Direct 6.25.21).

1080. Dyke 1999, Marriott 2001, and Muller 1998, in combination with the '358 Patent, would not have provided any motivation to the POSA to make a method of treatment for psoriasis comprising apremilast because the POSA would not have known about apremilast.

Trial Tr. at 1372:7–21; 1376:19–1377:3 (Davies Direct 6.23.21); 1700:25–1701:23 (Knowles Direct 6.25.21).

1081. Dyke 1999, Marriott 2001, and Muller 1998, in combination with the ’358 Patent, would not have provided any motivation to the POSA to make a method of treatment for psoriasis comprising apremilast with a reasonable expectation of success because there was no pharmacological data in Dyke 1999, Marriott 2001 or Muller 1998, or any other reference available prior to March 2002, to suggest that apremilast would have been suitable for use in a method of treating psoriasis. Trial Tr. at 1372:7–21, 1375:9–1376:1, 1376:19–1377:3 (Davies Direct 6.23.21); 1701:18–1702:2 (Knowles Direct 6.25.21).

a) Defendants’ alleged prior art references

(1) ’358 Patent

1082. The facts concerning the ’358 Patent are incorporated here by reference. *See generally* PF ¶¶ 302–33.

(2) Dyke 1999

1083. Dyke 1999 (JTX-67) is a summary review article on the therapeutic potential of PDE4 inhibitors as of 1999. Trial Tr. at 1373:1–7 (Davies Direct 6.23.21); *see* JTX-67 at JTX-67_1.

1084. Dyke 1999 describes a large number of different classes of compounds. Trial Tr. at 1373:8–10 (Davies Direct 6.23.21).

1085. Dyke 1999 does not disclose apremilast or any of the compounds of Formula I of the ’358 Patent. Trial Tr. at 1372:7–19 (Davies Direct 6.23.21); 1694:20–23 (Knowles Direct 6.25.21).

1086. Dyke 1999 does not disclose any of the properties of apremilast or any of the compounds of Formula I of the ’358 Patent. Trial Tr. at 1372:7–19 (Davies Direct 6.23.21).

1087. Dyke 1999 reports that nausea and emesis are the two "side effects most commonly associated with selective PDE4 inhibitors[.]" Trial Tr. at 1695:13–19 (Knowles Direct 6.25.21); JTX-67 at JTX-67_5–7.

1088. Dr. Page testified that the compound Ro20-1724 had been shown to have "modest benefit" in the treatment of psoriatic lesions. Trial Tr. at 712:22–713:1 (Page Direct 6.18.21); JTX-67 at JTX-67_12.

1089. Dyke 1999's discussion of Ro20-1724 concerns topical, not oral, administration. Trial Tr. at 1697:13–16 (Knowles Direct 6.25.21); JTX-67 at JTX-67_12.

1090. Topical administration is a local form of administration that is intended to have an effect at the site where the drug is placed. Trial Tr. at 1697:17–1698:1 (Knowles Direct 6.25.21). In contrast, oral administration is intended to have a systemic effect by exposing the whole body to the drug. Trial Tr. at 1697:17–1698:1 (Knowles Direct 6.25.21).

1091. Showing modest benefit as a topical treatment would not tell the POSA whether a compound was suitable for oral administration. Trial Tr. at 1698:2–5 (Knowles Direct 6.25.21).

1092. Ro20-1724 is not a thalidomide analog. Trial Tr. at 1698:6–9 (Knowles Direct 6.25.21).

1093. Dyke 1999 does not specifically state that apremilast is a PDE4 inhibitor useful in treating psoriasis. Trial Tr. at 1695:3–5 (Knowles Direct 6.25.21); 783:15–19 (Page Cross 6.18.21).

1094. Dyke 1999 states that "[t]o date, the clinical data in most therapeutic areas with compounds of this class is inconclusive," meaning that the POSA would not have believed that Dyke was promising success with these compounds. Trial Tr. at 1698:10–19 (Knowles Direct 6.25.21); JTX-67 at JTX-67_14.

(3) Marriott 2001

1095. Marriott 2001 (JTX-66) is a summary review article that discusses thalidomide analogs. Trial Tr. at 1698:23–24 (Knowles Direct 6.25.21); JTX-66 at JTX-66_1.

1096. Marriott 2001 is an article from Celgene. Trial Tr. at 1372:12–21 (Davies Direct 6.23.21); JTX-66 at JTX-66_1.

1097. Marriott 2001 was published after the ’358 Patent was published. Trial Tr. at 1373:15–1374:2 (Davies Direct 6.23.21).

1098. Dr. Page did not identify Marriott 2001 himself, this document was provided to him by counsel. Trial Tr. at 782:16–19 (Page Cross 6.18.21).

1099. Marriott 2001 does not disclose apremilast or any of the compounds of Formula I of the ’358 Patent. Trial Tr. at 1372:7–19 (Davies Direct 6.23.21).

1100. Marriott 2001 does not disclose the properties of apremilast or any of the compounds of Formula I of the ’358 Patent. Trial Tr. at 1372:7–19 (Davies Direct 6.23.21).

1101. Marriott 2001 does not specifically state that apremilast is a PDE4 inhibitor useful in treating psoriasis. Trial Tr. at 1699:20–22 (Knowles Direct 6.25.21); 783:25–784:3 (Page Cross 6.18.21) (“Q. And you didn’t point to any statement in Marriott 2001 specifically stating that apremilast is a PDE4 inhibitor useful in treating psoriasis? A. That’s correct. I talked about other PDE4 inhibitors.”).

1102. Marriott 2001 notes that “[t]he side effect profile (that includes teratogenicity and neuropathy), the low aqueous solubility and the poor aqueous stability of thalidomide may impose limits on the dose that can be tolerated.” JTX-66 at JTX-66_3.

1103. Marriott 2001 rejects the suggestion that “the administration of a single thalidomide enantiomer rather than the racemic mixture would improve the side effect profile,” because ”thalidomide rapidly undergoes racemization under both *in vitro* and *in vivo*

conditions, ***making administration of a single isomer non-viable***." JTX-66 at JTX-66_3–4 (emphasis added).

1104. Marriott 2001, JTX-66, describes safety concerns related to thalidomide analogs. Trial Tr. at 1372:20–21 (Davies Direct 6.23.21); 1700:9–10 (Knowles Direct 6.25.21).

1105. Marriott 2001 states that, thalidomide analogs might be useful for therapeutic areas with little or no clinical options available, even though the analogs were potentially teratogenic. Trial Tr. at 1374:20–1375:6 (Davies Direct 6.23.21); 1749:3–1750:5 (Alexis Direct 6.25.21); JTX-66 at JTX-66_7 ("Bearing in mind the potential clinical efficacy of thalidomide in a range of conditions with very little therapeutic option it is an exciting prospect that these novel compounds [thalidomide analogs] may provide us with a new generation of clinically effective drugs.").

1106. Marriott 2001 describes the inhibition of PDE4 by several compounds. JTX-66 at JTX-66_5.

1107. Marriott 2001 recognizes that "[o]ne of the major side effects observed for PDE4 inhibitors evaluated in the clinic has been emesis." JTX-66 at JTX-66_6.

1108. Marriott 2001 states that, for thalidomide analogs, "no data concerning clinical efficacy has yet been published." Trial Tr. at 1700:2–8 (Knowles Direct 6.25.21); JTX-66 at JTX-66_7; JTX-66_6.

1109. Marriott 2001 reports that the SelCID compound CDC-998 had begun clinical development, but no reference in the prior art, including Marriott 2001, provided the structure of CDC-998. Trial Tr. at 1699:6–10 (Knowles Direct 6.25.21).

1110. Norman 2002 confirms that the structure of CDC-998 was not available to the public as of 2002. JTX-282 at JTX-282_2 (Table 1, n. C).

1111. There is no evidence in the record that Celgene ever published the structure of CDC-998.

1112. Without knowing the structure of a compound, the POSA would not have had any interest in pursuing further development or modification of that compound. Trial Tr. at 1699:11–15 (Knowles Direct 6.25.21).

1113. Marriott 2001 reports that CDC-801 had successfully completed two Phase I clinical studies in the UK. JTX-66 at JTX-66_6. Internal Celgene documents demonstrate that the Phase I clinical studies discussed in Marriott 2001 for CDC-801 were conducted only in males. Trial Tr. at 161:20–162:6, 162:12–19 (Schafer Direct 6.14.21); PTX-940 at PTX-940_68, PTX-940_70.

1114. Marriott 2001 also reports that CDC-998 had begun Phase I clinical studies. JTX-66 at JTX-66_6. CDC-998 was only tested in men and/or surgically sterilized and/or postmenopausal women, and was never tested in women of childbearing potential. Trial Tr. at 162:20–163:3 (Schafer Direct 6.14.21).

1115. Marriott 2001 observes that the "success ***or failure*** of these [thalidomide analogs] as pharmaceuticals" will only be known in the "next few years." JTX-66 at JTX-66_7.

1116. Marriott 2001 states that "far more data are required concerning the mechanisms of action of these compounds and the cellular targets that characterise their activities" and "safety concerns associated with thalidomide will have to be closely monitored during use of the analogues." Trial Tr. at 1374:9–19 (Davies Direct 6.23.21); JTX-66 at JTX-66_7.

(4) Muller 1998

1117. Muller 1998, JTX-69, is a summary review article that discusses thalidomide analogs. Trial Tr. at 1693:20–21 (Knowles Direct 6.25.21); JTX-69 at JTX-69_1.

1118. Muller 1998 is an article from Celgene. Trial Tr. at 1372:12–19 (Davies Direct 6.23.21); JTX-69 at JTX-69_1.

1119. Muller 1998 (JTX-69) does not disclose apremilast or any of the compounds of Formula I of the '358 Patent. Trial Tr. at 1372:7–19 (Davies Direct 6.23.21).

1120. Muller 1998 does not disclose any of the properties of apremilast or any of the compounds of Formula I of the ’358 Patent. Trial Tr. at 1372:7–19 (Davies Direct 6.23.21).

1121. Muller 1998 generally summarizes the relationship between PDE4 inhibition, TNFα, and certain disease states, but does not mention psoriasis. JTX-69.

1122. Muller 1998 does not specifically state that apremilast is a PDE4 inhibitor useful in treating psoriasis. Trial Tr. at 1694:16–18 (Knowles Direct 6.25.21); 783:20–24 (Page Cross 6.18.21) (“Q. You didn’t point to any statement in Muller 1998 specifically stating that apremilast is a PDE4 inhibitor that’s useful in treating psoriasis? A. That’s correct. I don’t think it is disclosed in Muller 1998.”).

1123. Dr. Page did not identify Muller 1998 himself, this document was provided to him by counsel. Trial Tr. at 782:20–22 (Page Cross 6.18.21).

b) The POSA would not have known about apremilast.

1124. The ’358 Patent (alone or in combination with Dyke 1999, Marriott 2001, and Muller 1998, or any other reference in the prior art) does not disclose or enable stereomerically pure apremilast. Trial Tr. at 1376:2–11 (Davies Direct 6.23.21).

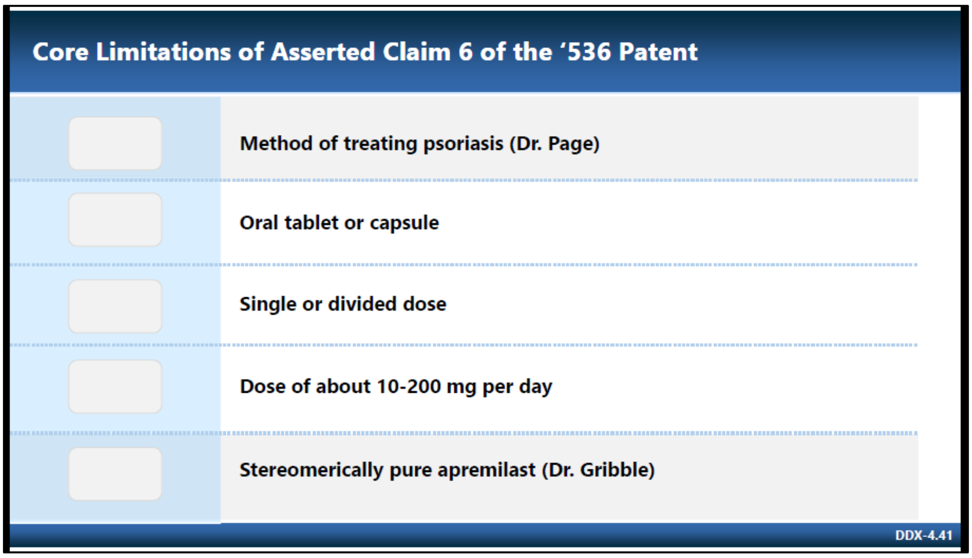
1125. As of March 2002, stereomerically pure apremilast was not publicly known. Trial Tr. at 1376:19–1377:3 (Davies Direct 6.23.21).

1126. A POSA would not have been motivated to use stereomerically pure apremilast as of December 2001, or March 2002 in a method of treatment of psoriasis, because a POSA would have been unaware of apremilast, and accordingly, any properties of stereomerically pure apremilast. Trial Tr. at 1376:19–1377:3 (Davies Direct 6.23.21).

1127. For at least these reasons, claim 6 of the ’536 Patent would not have been obvious to a POSA as of March 2002. Trial Tr. at 1376:19–1377:3 (Davies Direct 6.23.21).

c) Defendants failed to identify any motivation to combine the ’358 Patent, with Dyke 1999, Marriott 2001, or Muller 1998.

1128. Dr. Gilmore purported to rely on Dr. Gribble for the limitation of stereomerically pure apremilast. *See* Trial Tr. at 867:12–14, 868:4–12 (Gilmore Direct 6.21.21); DDX-4.41 (reprinted below), but Dr. Gribble did not opine on whether stereomerically pure apremilast would have been obvious over the ’358 Patent alone, or in combination with Dyke 1999, Marriott 2001, or Muller 1998.



1129. Dr. Gribble did not discuss Dyke 1999 or Muller 1998 at all during his testimony.

1130. Dr. Gilmore did not attempt to analyze how the POSA would have interpreted the prior art with respect to the obviousness of “stereomerically pure apremilast”. Trial Tr. at 830:6–9, 867:20–23 (Gilmore Direct 6.21.21)

1131. Dr. Page is not a chemist, and did not attempt to analyze how the POSA would have interpreted the prior art with respect to the obviousness of “stereomerically pure apremilast”. Trial Tr. at 722:4–8 (Page Direct 6.18.21); 744:17–19, 745:2–4 (Page Cross 6.18.21).

d) The POSA would not have reasonably expected that apremilast had any desirable properties.

1132. As of March 2002, the POSA would not have had any reason to reasonably expect that Example 12, or either enantiomer of Example 12, let alone apremilast, would have desirable biological properties, like potency, safety, tolerability, or other drug-like properties. Trial Tr. at 1370:3–11 (Davies Direct 6.23.21).

1133. There was no information in the published literature about the potency, selectivity, safety, tolerability (therapeutic window, side effect profile) or drug-like properties of any of the compounds of Formula I of the ’358 Patent, let alone the any of 17 example compounds, including Example 12. Trial Tr. at 1317:5–8, 1372:12–19 (Davies Direct 6.23.21).

1134. Given the complete lack of biological data concerning any of the compounds of Formula I of the ’358 Patent, the POSA would not have reasonably expected that Example 12 or either of the enantiomers of Example 12, much less apremilast in particular, would have the therapeutic window, be safe, and have drug-like properties, that would make it suitable for use in a method of treatment of psoriasis. Trial Tr. at 1366:9–16, 1372:12–19 (Davies Direct 6.23.21); 1692:20–1693:3 (Knowles Direct 6.25.21).

1135. A POSA could not have extrapolated biological data trends from compounds that share similar structural features to apremilast because the POSA would have had no data for any of the compounds of Formula I of the ’358 Patent. Trial Tr. at 1368:5–11 (Davies Direct 6.23.21).

1136. Information from either Muller 1998 or Marriott 2001 (or any other data specifically concerning thalidomide analogs other than those in the ’358 Patent) does not bear on the suitability of apremilast to be used in a method of treating psoriasis. Trial Tr. at 1701:8–17 (Knowles Direct 6.25.21).

1137. There was no data in Muller 1998, Marriott 2001, or any other reference available before March 2002 that would have provided a POSA with any reasonable

expectation regarding apremilast's ability to be successfully used as a treatment for psoriasis. Trial Tr. at 1701:8–17 (Knowles Direct 6.25.21).

1138. Marriott 2001, noting that "[o]ne of the major side effects observed for PDE4 inhibitors evaluated in the clinic has been emesis," observes that a different SelCID, CDC-998, had been brought into Phase I trials, and showed "no emetic effects." JTX-66 at JTX-66_6.

1139. Marriott 2001 does not report the dose levels at which emesis was examined for CDC-998, which makes Marriott 2001's information on emetic effects "of limited value." Trial Tr. at 1729:18–23 (Knowles Cross 6.24.21); JTX-66 at JTX-66_6.

1140. As previously explained, without a reported structure for CDC-998, the POSA would not have been interested in CDC-998. Trial Tr. at 1699:11–15 (Knowles Direct 6.25.21).

e) The POSA would not have been motivated to use apremilast or have had a reasonable expectation that it would be useful in treating psoriasis.

1141. Having apremilast in hand would not have put the POSA in possession of any data about apremilast. Trial Tr. at 1692:6–8 (Knowles Direct 6.25.21). The POSA would have had no knowledge of its potency, safety, tolerability, selectivity, or drug-like properties. Trial Tr. at 1692:6–19 (Knowles Direct 6.25.21).

1142. Having apremilast in one hand and the '358 Patent in the other, the POSA would not have been able to draw any conclusion about apremilast from the '358 Patent. Trial Tr. at 1692:20–24 (Knowles Direct 6.25.21).

1143. Without data for apremilast, the POSA would not have been motivated to use apremilast as part of a method of treatment for psoriasis, with a reasonable expectation of success, given the complete absence of data about apremilast in the prior art and the POSA's concern about apremilast's connection to thalidomide. Trial Tr. at 1368:12–21 (Davies Direct 6.23.21); 1691:16–25 (Knowles Direct 6.25.21).

1144. Dr. Gilmore did not offer any testimony regarding apremilast's association with thalidomide, or the impact such association would have had on the POSA's motivation to use apremilast as a part of a method of treatment for psoriasis with a reasonable expectation of success.

f) Marriott 2001 would have led the POSA to avoid thalidomide analogs.

1145. Marriott 2001 would have suggested to the POSA that thalidomide analogs may *not* be suitable for use in a methods of treating psoriasis. Trial Tr. at 1376:19–1377:3 (Davies Direct 6.23.21).

1146. As explained above, Marriott 2001 details safety concerns related to thalidomide. PF ¶¶ 1095–1116; *see also* JTX-66 at JTX-66_7.

1147. Apremilast's relationship to thalidomide would have caused a POSA to be concerned regarding the potential for teratogenic effects—a significant safety concern. Trial Tr. at 1326:19-24 (Davies Direct 6.23.21).

1148. The well-known side effects of thalidomide would have been no different in the early 2000s than earlier in time. Trial Tr. at 1747:17–1748:6 (Alexis Direct 6.25.21).

1149. Dermatologists heavily value the overall quality-of-life impact of therapies, and will weigh the favorable benefit of a treatment against minimizing safety and tolerability issues. Trial Tr. at 1750:23–1751:10 (Alexis Direct 6.25.21).

1150. The POSA would not have reasonably expected that a thalidomide analog would be safer than existing treatments for psoriasis in 2002. Trial Tr. at 1751:11–13 (Alexis Direct 6.25.21).

1151. In the early 2000s, the POSA would have come to the conclusion that the risks associated with thalidomide far outweigh any potential benefits for the treatment of a condition like psoriasis. Trial Tr. at 1747:17–1748:6 (Alexis Direct 6.25.21).

1152. The uses for which thalidomide was reintroduced to the market, including treating severe diseases such as to leprosy where there were few if any alternative treatments, would not have led the POSA to consider thalidomide's use for psoriasis. Trial Tr. at 1748:7–1749:2 (Alexis Direct 6.25.21); JTX-66 at JTX-66_7.

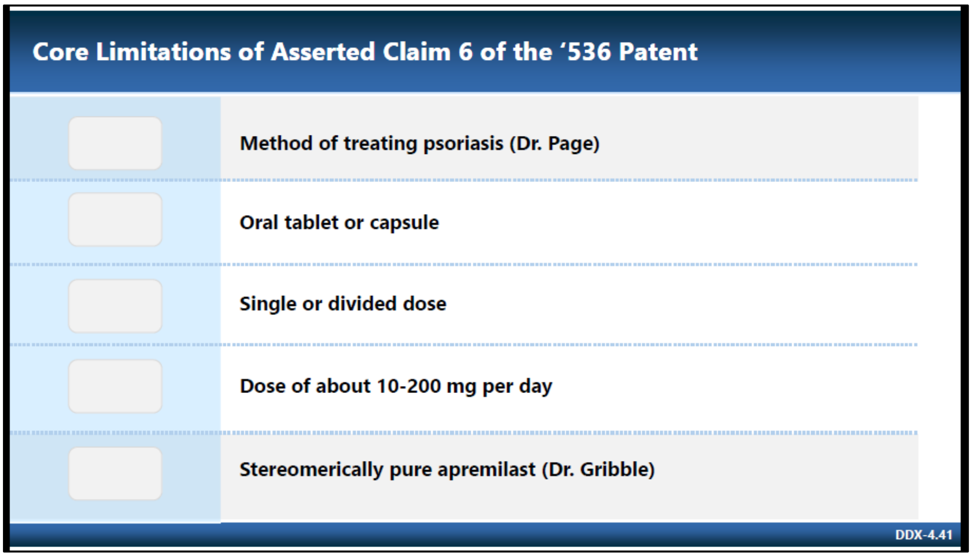
1153. The asserted claim of the '536 Patent would not have been obvious in view of the '358 Patent in combination with Dyke 1999, Marriott 2001, and Muller 1998 as of March 2002. Trial Tr. at 1700:18–1702:2 (Knowles Direct 6.25.21); 1376:19–1377:2 (Davies Direct 6.23.21).

6. Defendants did not adduce proof relevant to any other combination.

1154. Defendants raised two additional obviousness combinations in their Pre-trial Brief, namely 1) '358 Patent, WO '606, Dyke 1999 and Marriott 2001; and 2) '358 Patent, WO '606, Dyke 1999 and Marriott 2001. (ECF No. 398 (Defendants' Pretrial Brief) at 38).

1155. Defendants did not adduce proof of either combination.

1156. Dr. Gilmore purported to rely on Dr. Gribble for the limitation of stereomerically pure apremilast, *see* DDX-4.41 (reprinted below), and Dr. Page for the method of treatment limitation. Trial Tr. at 867:12–14; 868:4–12 (Gilmore Direct 6.21.21)



1157. Dr. Page did not opine on whether the method of treatment limitation would have been obvious over the ’358 Patent in combination with WO ’606, Dyke 1999, or Marriott 2001; or the combination of the ’358 Patent in combination with Takeuchi, Dyke 1999, or Marriott 2001.

1158. Neither Dr. Gilmore or Dr. Page addressed WO ’606 or Takeuchi during their respective testimonies.

1159. Dr. Gribble did not discuss Dyke 1999 during his testimony.

1160. Defendants’ experts offered no testimony on the motivation to combine the references in either of the two combinations they briefed in their Pre-Trial Brief.

1161. Dr. Gilmore did not attempt to analyze how the POSA would have interpreted the prior art with respect to the obviousness of “stereomerically pure apremilast”. Trial Tr. at 830:6–9, 867:20–23 (Gilmore Direct 6.21.21)

1162. Dr. Page is not a chemist, and did not attempt to analyze how the POSA would have interpreted the prior art with respect to the obviousness of “stereomerically pure apremilast.” Trial Tr. at 722:4–8 (Page Direct 6.18.21); 744:17–19; 745:2–4 (Page Cross 6.18.21).

7. Objective indicia

1163. The objective indicia discussed above in connection with the asserted claims of the ’638 Patent are incorporated by reference. *See* PF ¶¶ 673–1010.

D. Defendants Have Failed to Prove that the ’536 Psoriasis Patent is Invalid for Lack of Written Description and Enablement.

1. Enablement

1164. None of Amgen’s experts have testified that clinical studies would have been needed to show the success of apremilast in a method of treatment.

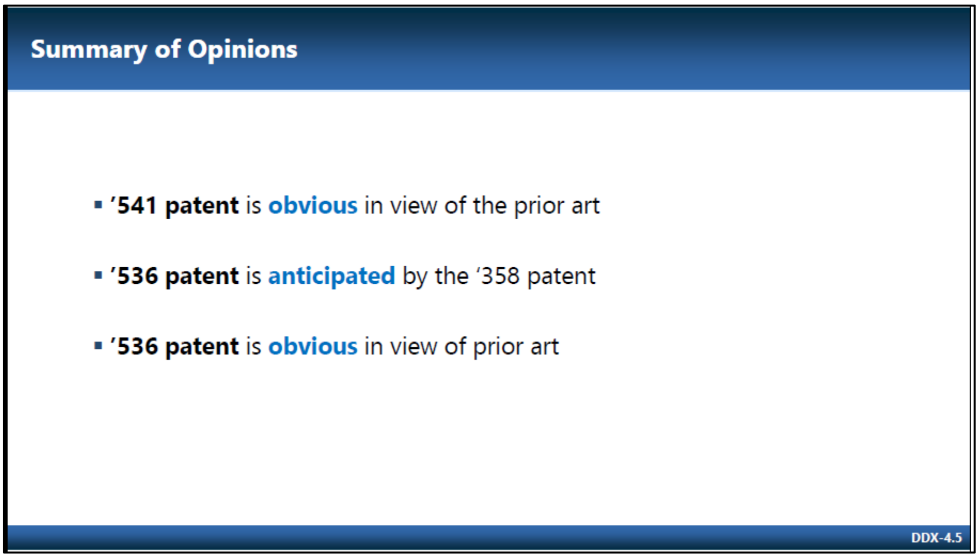
1165. Amgen’s expert Professor Knowles testified that he did not conclude that any prior art reference failed to render claim 6 of the ’536 Patent obvious simply because it failed

to disclose human clinical data teaching a therapeutically effective amount of apremilast to treat diseases and disorders ameliorated by the inhibition of PDE4, including psoriasis. Trial Tr. at 1700:17–24 (Knowles Direct 6.25.21).

1166. None of defendants' experts offered testimony or other evidence that claim 6 of the '536 Patent is invalid because of a lack of enablement.

1167. Dr. Gilmore did not state the words "written description" or "enablement" at any point during her testimony.

1168. During her testimony, Dr. Gilmore said that the scope of the opinions she would be discussing are summarized as follows: "that the '541 Patent is obvious in view of the prior art; that the '536 Patent is anticipated by the '358 Patent, and that the '536 Patent is obvious in view of the prior art." Trial Tr. at 820:7–15 (Gilmore Direct 6.21.21); DDX-4.5 (reprinted below).



1169. Dr. Gilmore did not analyze claim 6 under the *Wands* factors.

1170. Dr. Gilmore testified that the '536 Patent would make it obvious to the POSA to start at a 10-milligram dose for the use of apremilast in a titration schedule for humans. Trial Tr. at 857:22–25 (Gilmore Direct 6.21.21).

1171. Dr. Gilmore testified that the ’536 Patent discloses a dosing regimen or dosing range of therapy using apremilast. Trial Tr. at 833:13–21 (Gilmore Direct 6.21.21).

1172. Dr. Gilmore testified that Claim 1 of the ’536 Patent “indicates a method of treating psoriasis” using a particular dosing range of apremilast. Trial Tr. at 833:22–834:2 (Gilmore Direct 6.21.21).

1173. Based on the ’536 Patent, the suitable dose and dose frequency of apremilast to administer “can be readily selected by those skilled in the art[.]” Trial Tr. at 1766:24–1767:10 (Alexis Direct 6.25.21); JTX-7 at 13:40–49.

1174. The ’536 Patent provides data for the LPS-lung neutrophilia ferret model, which shows a therapeutic index of 12 for apremilast. JTX-7 at 26:50–29:19 (Example 8).

1175. The LPS Ferret study “is a very good model for measuring emesis.” Trial Tr. at 792:23–793:2 (Page Redirect 6.18.21).

1176. The purpose of LPS-lung neutrophilia ferret model is to provide information about the dose level at which LPS-induced inflammation is reduced, and the dose level at which emesis may be observed — which allows calculation of the therapeutic index. JTX-7 at 29:5–8.

1177. Claim 6 of the ’536 Patent is enabled. JTX-7.

1178. **The nature of the invention**: The Asserted Claim of the ’536 Patent is directed to methods of treating psoriasis, by orally administering 10–200 mg per day of 97% stereomerically pure apremilast in a tablet or capsule. JTX-7 at cls. 1, 6.

1179. **The breadth of the claims**: The Asserted Claim of the ’536 Patent is directed to methods of treating psoriasis, by orally administering 10–200 mg per day of 97% stereomerically pure apremilast in a tablet or capsule as a either a single dose or a divided dose. JTX-7 at cls. 1, 6.

1180. The term “autoimmune diseases” is not in the Asserted Claim.

1181. The term "therapeutically effective amount," is not in the Asserted Claim.

1182. The Asserted Claim of the '536 Patent defines a dose of 10–200 mg/day of apremilast administered in the form of a tablet or capsule. JTX-7 at cls. 1, 6.

1183. The Asserted Claim of the '536 Patent limits the disease state to psoriasis. JTX-7 at cls. 1, 6.

1184. **The state of the prior art**: The prior art was replete with examples of somewhat potent PDE4 inhibitors that were introduced for use in a number of different disease states, including psoriasis, which could be combined with the specific guidance in the '536 Patent specification. Trial Tr. at 711:9–16; 712:20–713:1 (Page Direct 6.18.21); 1680:21–1682:10 (Knowles Direct 6.25.21); *see also* JTX-67.

1185. **Relative skill of those in the art**: Under either parties' definition, the POSA's skill level would be high Trial Tr. at 587:13–588:1 (Gribble Direct 6.18.21); 1300:23–1301:11 (Davies Direct 6.23.21).

1186. **The amount of direction or guidance in the patent specification**: The '536 Patent specification discloses dose ranges and significant amounts of pre-clinical data, which confirm the potency of apremilast in numerous *in vitro* and *in vivo* assays, as well as information about apremilast's therapeutic index in ferrets. *E.g.*, JTX-7 at 16:1–18, 22:23–29:19.

1187. The specification of the '536 Patent presents information for the dose amounts of apremilast needed to treat psoriasis. *See* JTX-7 at 16:1–18.

1188. **The predictability or unpredictability in the field**: Although drug discovery may be unpredictable in the abstract, this case is not an abstract case, because the patent specification provides significant quantities of data on apremilast's suitability for use in a method of treating psoriasis. JTX-7 at 22:23–29:19 (Examples 3–8: providing *in vivo* and *in vitro* data), *see also* 29:21–30:61 (Examples 9–11: discussing specific dosage forms).

1189. The Asserted Claim also identifies a particular dose range, of 10-200 mg/day. JTX-7 at 14:37–64.

1190. **The presence or absence of working examples**: There is additional information in the patent specifications beyond the LPS lung neutrophilia ferret model. The ’536 Patent specification includes data that defines the potency of apremilast against PDE4 and TNFα in numerous *in vitro* and *in vivo* models. JTX-7 at 22:23–29:19 (Examples 3–8).

1191. The ’536 Patent specification discloses dosing ranges, including an example dosing range of 10 mg to 200 mg, JTX-7 at 13:37–64, and example dosage forms, including, e.g., a 200 or 100 mg oral dosage form, JTX-7 at 29:21–30:30 (Examples 9 and 10).

1192. **The quantity of experimentation**: The specification provides dosing ranges, including an example dosing range of 10 mg to 200 mg. JTX-7 at 14:37–64.

1193. The specification provides numerous examples of *in vivo* (in mouse and ferret) and *in vitro* data. JTX-7 at 23:24–29:18, *see also id.* at 29:21–30:61 (discussing specific dosage forms).

1194. The data available in the ’536 Patent would have helped the POSA in predicting the dose range that would be effective in human studies. Trial Tr. at 239:8–19 (Knowles Direct 6.15.21).

1195. Amgen raised a Motion for Judgment on Partial Findings on the issue of enablement and written description of the ’536 Patent in open court on June 22, 2021, and later submitted a memorandum in support of this motion. (ECF. No. 462).

2. Written description

1196. The facts set forth in the immediately above section are incorporated by reference. PF ¶¶ 164–95.

1197. None of defendant’s experts offered testimony or other evidence that claim 6 of the ’536 Patent is invalid because of a lack of written description. the specification of the ’536

Patent fails to sufficiently describe the invention such that the POSA would have understood the inventors were in possession of the claimed subject matter.

1198. Claim 6 of the '536 Patent is supported by adequate written description. JTX-7.

1199. The specification of the '536 Patent discusses using therapeutically effective amounts of apremilast to treat diseases and disorders ameliorated by the inhibition of PDE4, including arthritis and psoriasis. *E.g.*, JTX-7 at 12:66–13:13.

1200. The specification of the '536 Patent discusses dosage amounts to be used of apremilast, including between 10 mg and 200 mg per day. *E.g.*, JTX-7 at 16:1–18.

1201. The specification of the '536 Patent includes recommended daily dose ranges "for the conditions described herein," which includes psoriasis. JTX-7 at 13:49–64; 7:62–8:8.

1202. The specification of the '536 Patent states that the dose and dose frequency may vary depending upon, among other factors, body weight. JTX-7 at 13:45–47.

1203. The specification of the '536 Patent provides example dosage forms, including, e.g., 200 or 100 mg oral dosage form. JTX-7 at 29:21–30:30 (Examples 9 and 10). The specification provides extensive *in vitro* and *in vivo* data outlining apremilast's ability to inhibit PDE4 and TNFα, as well as further information supporting apremilast's large therapeutic window relating to emesis and nausea. *E.g.*, JTX-7 at 22:23–29:19.

XII. THE ASSERTED CLAIMS OF THE '101 FORM B PATENT ARE INFRINGED AND NOT INVALID

A. Person of Ordinary Skill in the Art

1204. The person of ordinary skill in the art for purposes of the '101 Patent is an individual with a bachelor's degree in chemistry, chemical engineering, or a related discipline, with some knowledge of crystalline solid forms and their characterization, and several years of experience in the pharmaceutical industry; or an advanced degree in the above listed disciplines, with some knowledge of solid-state chemistry or analytical chemistry and less

experience. Trial Tr. at 437:7–21 (Myerson Direct 6.16.21); 1587:25–1588:4 (Myerson Direct 6.24.21).

1205. The person of ordinary skill in the art for purposes of the ’101 Patent is the same as the POSA for the ’283 Patent. Trial Tr. at 437:7–21 (Myerson Direct 6.16.21); 1587:25–1588:4 (Myerson Direct 6.24.21).

1206. The definition of a POSA offered by Amgen’s expert, Prof. Myerson, differs slightly from the definition proposed by Defendants’ expert, Prof. Steed, and Zydus’s expert, Dr. Sacchetti. Trial Tr. at 1588:5–10 (Myerson Direct 6.24.21)

1207. Prof. Myerson’s opinions would not have been different had he applied Prof. Steed’s or Dr. Sacchetti’s definitions. Trial Tr. at 1588:8–10 (Myerson Direct 6.24.21).

B. Technology Background

1208. A crystal is a solid where the atoms and molecules are arranged into a repeating three-dimensional lattice arrangement. Trial Tr. at 425:17–426:4 (Myerson Direct 6.24.21).

1209. For a crystal, the unit cell is the smallest arrangement of the atoms that are repeating. Trial Tr. at 425:17–426:4 (Myerson Direct 6.16.21). The unit cell determines the crystalline form.

1210. Crystallization is the process of making a crystal; a common example of crystallization is making rock candy. Trial Tr. at 426:5–18 (Myerson Direct 6.16.21).

1211. Polymorphism occurs when a given atom or molecule can crystallize into more than one crystalline form. Trial Tr. at 426:19–427:9 (Myerson Direct 6.16.21).

1212. When more than one unique crystalline form is created for of a given compound, those crystalline structures are referred to as polymorphs. Trial Tr. at 426:19–427:23 (Myerson Direct 6.16.21).

1213. A solvate is a unique crystalline form, or polymorph, of a given compound, wherein a solvent is part of the repeating crystal structure. Trial Tr. at 427:24–428:8 (Myerson Direct 6.16.21).

1214. A hydrate is a solvate, wherein the solvent is water. Trial Tr. at 427:24–428:8 (Myerson Direct 6.16.21).

1215. If a pharmaceutical drug is polymorphic, the crystalline form of that pharmaceutical drug may impact its properties, including its solubility, dissolution rate, hygroscopicity, and chemical stability. Trial Tr. at 428:9–428:23 (Myerson Direct 6.16.21).

1216. Solubility and dissolution rate, which vary between crystalline forms, can directly impact bioavailability of the pharmaceutical drug. Trial Tr. at 428:9–23 (Myerson Direct 6.16.21).

1217. Hygroscopicity, which is whether a crystalline form absorbs water from the atmosphere, can affect manufacturability and shelf life of the pharmaceutical drug. Trial Tr. at 428:9–23 (Myerson Direct 6.16.21).

1218. Chemical stability can also affect shelf life of the pharmaceutical drug. Trial Tr. at 428:9–23 (Myerson Direct 6.16.21).

1219. X-ray Powder Diffraction ("XRPD") is an analytical technique wherein X-rays are shone on a powder sample of interest and the X-rays diffract based on how the molecules are stacked in the crystal. Trial Tr. at 428:25–429:20 (Myerson Direct 6.16.21).

1220. An XRPD analysis results in X-ray diffraction which is measured by a diffractometer. The relationship between the wavelengths and the interplanar spacing is given by Bragg's law, and the result is a "diffractogram," a graphical depiction of the measured X-ray diffraction, examples of which can be seen in Figure 5 of the '101 Patent, JTX-5 at JTX-5_9, and in Dr. Gozzo's experimental data, e.g., PTX-1238 at PTX-1238_6. Trial Tr. at 430:22–431:16 (Myerson Direct 6.16.21).

1221. The error range for XRPD, both for the industry in general and for the ’101 and ’283 Patents in particular, is plus or minus 0.2 degrees 2-theta. Trial Tr. at 431:17–22 (Myerson Direct 6.16.21); *see also* JTX-5 at 51:65–67; JTX-6 at 51:38–40.

1222. Data from an XRPD analysis can be displayed as a diffractogram or as a peak list. Modern diffractometers generate the peak list from the diffractogram using software. Trial Tr. at 431:23–432:17 (Myerson Direct 6.16.21).

1223. XRPD is used in the pharmaceutical industry with respect to crystalline forms to determine which crystalline form of a given compound has been made and to verify that a crystalline form is being made reproducibly. Trial Tr. at 429:21–25 (Myerson Direct 6.16.21).

1224. Laboratory X-ray tubes and a synchrotron particle accelerator are two different X-ray sources that can be used in an XRPD analysis. XRPD using laboratory X-ray tubes as the X-ray source is called “laboratory XRPD” and XRPD using a synchrotron particle accelerator as the X-ray source is called “synchrotron XRPD.” Trial Tr. at 430:5–21 (Myerson Direct 6.16.21).

1225. As compared to laboratory-XRPD, synchrotron-XRPD provides more intense and sharper peaks and can detect the presence of a particular crystalline form in a mixture at a lower amount because of the intense nature of the synchrotron X-rays. Trial Tr. at 430:5–21 (Myerson Direct 6.16.21); 1268:8–10, 1269:21–1270:3 (Miller Cross 6.22.21).

1226. XRPD can detect if the sample being analyzed contains a mixture of crystalline forms, meaning it can detect if more than one crystalline form of a compound or another compound is present in a given sample. Trial Tr. at 430:1–4, 432:18–20 (Myerson Direct 6.16.21).

1227. If a mixture of crystalline forms are present in a sample being analyzed by XRPD, the resulting diffractogram will have peaks that are generated by both crystalline forms; peaks that are unique to only one crystalline form will be generated only by that form, and

peaks that are in common to more than one form in the mixture will have contributions from all forms in the mixture that generate that peak. Trial Tr. at 432:18–433:15 (Myerson Direct 6.16.21); 1147:14–1148:17 (Steed Cross 6.22.21).

1228. The limit of detection is the smallest detectable amount of a particular substance, or peak in that substance, given the instrumentation and procedures used, for example laboratory- or synchrotron-XRPD. Trial Tr. at 434:6–22 (Myerson Direct 6.16.21).

1229. A crystalline form can be present in a mixture or in a sample, but if it is present in a quantity below the limit of detection for the XRPD system used to analyze it, the peaks associated with that crystalline form will not be detected even though the crystalline form is present. Trial Tr. at 433:16–435:4 (Myerson Direct 6.16.21).

1230. A single XRPD peak may be used to identify a crystalline form in a mixture as long as that single peak is unique to the crystalline form that, as compared to any other crystalline form that could be present, meaning that the peak is not present in the other forms that could be in the sample. Trial Tr. at 435:5–12 (Myerson Direct 6.16.21).

C. Sandoz Infringes Claims 1 and 15 of the ’101 Form B Patent.

1231. On March 21, 2018, Sandoz submitted ANDA No. 211658 (“the Sandoz ANDA”) to the FDA under 21 U.S.C. § 355(j). FDA accepted for review Sandoz’s ANDA. SSF (A3) ¶ 1 (ECF No. 422).

1232. The Sandoz ANDA included a Paragraph IV Certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the ’101 Patent is invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Sandoz’s ANDA Products. SSF (A3) ¶ 2 (ECF No. 422).

1233. The Sandoz ANDA references Amgen’s NDA No. 205437 and seeks approval to market a generic version of 10 mg, 20 mg, and 30 mg Otezla tablets (collectively, “Sandoz’s ANDA Products”). SSF (A3) ¶ 4 (ECF No. 422).

1234. The submission of Sandoz's ANDA to the FDA seeking approval for Sandoz's ANDA is an act of infringement with respect to claims 1 and 15 of the '101 Patent under 35 U.S.C. § 271(e)(2)(A), if those claims are not found to be invalid or unenforceable. Civ. No. 18-11026, ECF No. 246. SSF (A3) ¶ 9 (ECF No. 422).

1235. Upon final approval of Sandoz's ANDA, the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Sandoz's ANDA Products will infringe claims 1 and 15 of the '101 Patent under 35 U.S.C. § 271(a), (b) and/or (c), if those claims are not found to be invalid or unenforceable. Civ. No. 18-11026, ECF No. 246. SSF (A3) ¶ 10 (ECF No. 422).

D. Zydus Infringes Claims 1 and 15 of the '101 Form B Patent.

1236. Defendant Zydus disputes infringement of claims 1 and 15 of the '101 Patent.

1. Zydus's ANDA Product

1237. On March 21, 2018, Defendant Zydus submitted ANDA No. 211859 ("the Zydus ANDA") to the FDA under 21 U.S.C. § 355(j), seeking approval from the FDA to sell its ANDA Product in the United States. ZSF (A2) ¶¶ 1, 5 (ECF No. 422).

1238. The Zydus ANDA included a Paragraph IV Certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that, in Zydus's opinion, the '101 Patent is invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Zydus's ANDA Products. ZSF (A2) ¶ 2 (ECF No. 422).

1239. Zydus's ANDA Products are tablets that contain apremilast as the active ingredient. Zydus's ANDA Products are a solid pharmaceutical composition that are to be formulated as 10 mg, 20 mg, and 30 mg tablets intended for oral administration. ZSF (A2) ¶¶ 4, 8, 10 (ECF No. 422).

1240. Zydus's ANDA Products also contain certain pharmaceutically acceptable excipients, including microcrystalline cellulose, low substituted hydroxypropyl cellulose,

copovidone, colloidal silicon dioxide, and magnesium stearate as excipients, ("Zydus's Excipients"), all of which comply with NF standards, indicating they are pharmaceutically acceptable excipients. ZSF (A2) ¶¶ 7, 9, 25 (ECF No. 422).

1241. The formulations of each dosage strength of Zydus's ANDA Products are described in the table below:

Sr. No.	Name of Ingredient	10 mg mg/unit	20 mg mg/unit	30 mg mg/unit	%w/w**	Function
Mixing and Blending						
1	Apremilast[@]	10.000	20.000	30.000	8.67	Active Ingredient
2	Microcrystalline Cellulose, NF [Avicel 102][@]	77.834	155.667	233.500	67.49	Diluent
3	Low Substituted Hydroxypropyl Cellulose, NF (L-HPC LH-21)	18.500	37.000	55.500	16.04	Diluent/ Disintegrant
4	Copovidone, NF (Kollidon VA 64)	4.333	8.667	13.000	3.76	Binder
5	Colloidal Silicon Dioxide, NF (Aerosil 200)	0.667	1.333	2.000	0.58	Glidant
Lubrication						
6	Magnesium Stearate, NF (Ligamed MF-2-K)	0.667	1.333	2.000	0.58	Lubricant
	Total (Core Tablets)	**112.000**	**224.000**	**336.000**	**97.11**	-
Film Coating Materials						
12	Opadry 20U580031 White[#]	3.333	--	--	2.89	Film Coating material
13	Opadry 20U570011 Tan[##]	--	6.667	--		
14	Opadry 20U520068 Yellow[###]	--	--	10.000		
15	Purified Water, USP[*]	q.s	q.s	q.s	--	Coating vehicle
	Total (Coated Tablets)	**115.333**	**230.667**	**346.000**	**100.000**	-

ZSF (A2) ¶ 8 (ECF No. 422); *see also* Trial Tr. at 459:15–460:11 (Myerson Direct 6.16.21); PTX-576 at PTX-576_8.

1242. Zydus's prescribing information states that Zydus's ANDA Product will be indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Zydus indicated in its ANDA that Zydus's

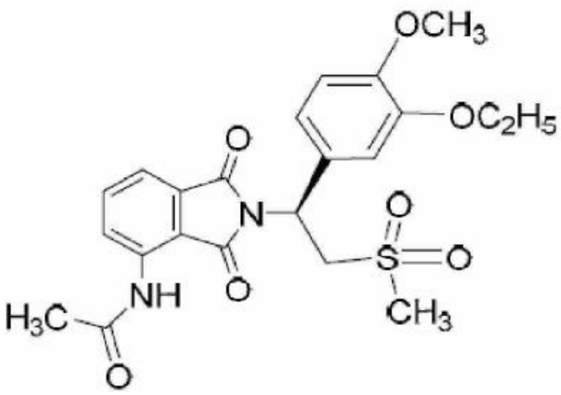
ANDA Products were developed as a generic drug equivalent to "Reference Drug Product [Otezla (apremilast) Tablets, 10 mg, 20 mg and 30 mg]." ZSF (A2) ¶ 5 (ECF No. 422).

1243. Zydus's ANDA Products are manufactured in India by Cadila Healthcare Limited ("Cadila"). ZSF (A2) ¶ 6 (ECF No. 422).

2. Zydus's API

1244. The active pharmaceutical ingredient ("API") in Zydus's ANDA Product is apremilast, which Zydus's ANDA gives the chemical name N-[2-[(lS)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-l,3-dioxo-lH-isoindol-4-yl] acetamide. ZSF (A2) ¶ 10 (ECF No. 422).

1245. Zydus reported the below structural formula for apremilast in its ANDA.



Apremilast

ZSF (A2) ¶ 11 (ECF No. 422).

1246. Zydus's apremilast drug substance is manufactured by Cadila as described in Drug Master File ("DMF") No. 032223. ZSF (A2) ¶ 12 (ECF No. 422).

1247. The manufacturing process for Zydus's drug substance API is set forth in its DMF. ZSF (A2) ¶ 13 (ECF No. 422).

3. The '101 Form B Patent

1248. Apremilast has several crystal forms, or polymorphs, including a polymorph referred to as "Form B." ZSF (A2) ¶ 16 (ECF No. 422).

1249. The ’101 Patent describes seven crystalline forms of apremilast, which are labeled in the patent as Form A through Form G. Trial Tr. at 448:11–22 (Myerson Direct 6.16.21); JTX-5 at 18:39–27:48.

1250. Form B, Form A, and Form F of apremilast are the only unsolvated crystalline forms of apremilast described in the ’101 Patent. Trial Tr. at 448:11–22 (Myerson Direct 6.16.21); JTX-5 at 19:8–9, 20:40–41, 25:59–60.

1251. Forms C, D, E, and G are solvates, meaning they have a solvent in their crystalline structure. Trial Tr. at 448:11–22 (Myerson Direct 6.16.21); JTX-5 at 21:66–22:1, 23:19–24, 24:46–50; 27:4–8.

1252. Form B of apremilast has an XRPD pattern comprising 2θ peaks at 10.1, 12.4, 13.5, 15.7, 16.3, 18.1, 20.7, 22.5, 24.7, 26.2, 26.9, and 29.1 degrees that are generated by Form B. ZSF (A2) ¶ 17 (ECF No. 422).

1253. The XRPD pattern for Form B is set forth in Figure 5 of the ’101 Patent. ZSF (A2) ¶ 18 (ECF No. 422); *see also* Trial Tr. at 438:14–24 (Myerson Direct 6.16.21); JTX-5 at JTX-5_9, JTX-5_41.

1254. The XRPD pattern for Form A is set forth in Figure 1 of the ’101 Patent. Trial Tr. 438:25–439:8 (Myerson Direct 6.16.21); JTX-5 at JTX-5_5, _41.

1255. The XRPD pattern for Form F is set forth in Figure 21 of the ’101 Patent. Trial Tr. 446:25–447:9 (Myerson Direct 6.16.21); JTX-5 at JTX-5_25, _41.

4. Stipulated claim limitations

1256. Zydus has stipulated that Zydus’s ANDA Products meet the claim limitation “which is enantiomerically pure,” as recited in claim 1 of the ’101 Patent, because the apremilast in Zydus’s ANDA Products is enantiomerically pure. ZSF (A2) ¶ 22 (ECF No. 422).

1257. Zydus has stipulated that the apremilast in Zydus’s ANDA Products meet the claim limitation “A solid pharmaceutical composition,” as recited in claim 15 of the ’101

Patent, because Zydus's ANDA Products are solid pharmaceutical compositions. ZSF (A2) ¶ 24 (ECF No. 422).

5. Zydus's API and ANDA Products contain "a Form B of [apremilast] . . . which has an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ."

1258. Zydus's Active Pharmaceutical Ingredient ("API") contains a mixture of Form A and Form B of apremilast. Trial Tr. at 439:9–25 (Myerson Direct 6.16.21).

1259. Testing of Zydus's API confirms that it contains Form B of apremilast that generates XRPD peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta. Trial Tr. at 439:9–21 (Myerson Direct 6.16.21) ; JTX-5 at cl. 1.

1260. Zydus's ANDA Products contain Zydus's API, which is a mixture of solid forms of apremilast, including Form B of apremilast that generates XRPD peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta, as well as Form A of apremilast. Trial Tr. at 439:9–21 (Myerson Direct 6.16.21); JTX-5 at cl. 1.

a) Independent testing of Zydus's API shows Form B is present in Zydus's API.

1261. Synchrotron-XRPD testing on samples of Zydus's API by Dr. Gozzo shows that Form B is present in Zydus's API. *See* PF ¶¶ 1264–1304.

1262. Claims 1 and 15 of the '101 Patent do not require a minimum amount of Form B of apremilast. Trial Tr. at 436:16–18 (Myerson Direct 6.16.21).

1263. The four XRPD peaks recited in claim 1 of the '101 Patent may have contributions from forms other than Form B, so long as they also have contributions from Form B of apremilast. Trial Tr. at 484:23–485:7 (Myerson Redirect 6.16.21).

(1) Overview of Dr. Gozzo's testing

1264. Zydus produced samples of Zydus API Batch Nos. AEA1MSJ01D, AEA1MSJ02D, and AEA1MSJ03D to Covington & Burling LLP. PTX-1115, ¶¶ 3, 5.

1265. Dr. Gozzo received samples of Zydus API Batch Nos. AEA1MSJ01D, AEA1MSJ02D, and AEA1MSJ03D from Covington and Burling. PTX-1246; PTX-1247; PTX-1253; PTX-1254; *see also* PTX-1115, ¶ 6.

1266. Dr. Fabia Gozzo performed independent testing on samples of Zydus's API by synchrotron-XRPD in June 2020. Trial Tr. at 440:3–441:9 (Myerson Direct 6.16.21); 496:18–497:17 (Gozzo Direct 6.16.21); *see also* Trial Tr. at 1229:24–25 (Miller Direct 6.22.21); PTX-1254.

1267. The samples that Dr. Gozzo prepared and analyzed by synchrotron-XRPD analysis as part of her analysis of samples of Zydus's API are listed in Table 3, below.

Table 3 - Zydus's API—Sample Description

ESS ID Code	Description	Sample Characteristics
FGCB54	Form B Reference Powder (CELGENE Apremilast API with lot number '1742S008')	1 capillary
FGCB81	Form A reference standard (Triclinic Labs reference number '897-14-1')	1 capillary
FGCB78	ZYDUS Apremilast API with Batch No: AEA1MSJ03D (ZYDAPR0022501)	3 capillaries: A, B, C
FGCB79	ZYDUS Apremilast API with Batch No: AEA1MSJ01D (ZYDAPR0019088)	3 capillaries: A, B, C
FGCB80	ZYDUS Apremilast API with Batch No: AEA1MSJ02D (ZYDAPR0022500)	3 capillaries: A, B, C

Trial Tr. at 440:8–441:14 (Myerson Direct 6.16.21); Trial Tr. at 506:4–507:1 (Gozzo Direct 6.16.21); PTX-1252; PTX-1253; *see also* PTX-1254, PTX-1255; PTX-1238 at PTX-1238_1–35, PTX-1239 at PTX-1239_44–83, PTX-1241 at PTX-1241_1, _6–12.

1268. Dr. Gozzo analyzed reference powders of Form A and Form B of apremilast by synchrotron-XRPD, and created diffractograms and peak lists for each. Trial Tr. at 502:16–504:1; 506:4–507:1 (Gozzo Direct 6.16.21); PTX-1238 at PTX-1238_1–8; PTX-1241 at PTX-1241_1, _12.

1269. The Form A reference powder analyzed by Dr. Gozzo was created and provided by a third party lab called Triclinic Labs. Triclinic Labs made the Form A reference powder by recrystallizing apremilast from a 10:1 ratio of ethanol to acetone and placed in a refrigerator for fast cooling. Trial Tr. at 464:14–465:18 (Myerson Cross 6.16.21); DTX-Zydus-56 at DTX-Zydus-56_4.

1270. The Form B reference powder is supplied by Celgene and is a sample of Celgene's apremilast API. Trial Tr. at 464:6–13 (Myerson Cross 6.16.21)

1271. Dr. Gozzo created an overlay of the experimental synchrotron-diffractograms for the Form A and Form B reference powders with a digitalized diffractogram (created using the industry-standard Uniscan IT computer program) for Form A and Form B, respectively, from the '101 Patent. Trial Tr. at 502:16–504:1 (Gozzo Direct 6.16.21); PTX-1238 at PTX-1238_1, _5.

1272. An overlay is when two diffractograms are placed on top of each other to compare them. Trial Tr. at 441:18–442:6 (Myerson Direct 6.16.21).

1273. Dr. Gozzo analyzed three samples from each of the three exhibit batches of Zydus's API [FGCB78A, B, C; FGCB79A, B, C; and FGCB80A, B, C] by synchrotron-XRPD, and created diffractograms and peak lists for each. Trial Tr. 504:2–506:3 (Gozzo Direct); PTX-1238 at PTX-1238_9–11; PTX-1239 at PTX-1239_44–82; PTX-1241 at PTX-1241_6–12.

1274. Dr. Gozzo created overlays comparing the experimental synchrotron-diffractograms for each of the three samples from each of the three Exhibit Batches of Zydus's API [FGCB78A, B, C; FGCB79A, B, C; and FGCB80A, B, C] to the experimental synchrotron-diffractograms for the Form A and Form B reference powders. Trial Tr. at 507:2–508:10 (Gozzo Direct 6.16.21); PTX-1238 at PTX-1238_18–35.

1275. Dr. Gozzo created a peak list for each sample analyzed by synchrotron-XRPD using TOPAS software, followed by a visual analysis to verify that every peak in the peak list

corresponds to a peak in the synchrotron-diffraction pattern. Trial Tr. at 504:22–505:22 (Gozzo Direct 6.16.21).

1276. Dr. Gozzo's tests, methodologies, and procedures were appropriate. Trial Tr. at 440:20–25 (Myerson Direct 6.16.21).

(2) The samples Dr. Gozzo tested of the Form A and Form B reference powders were samples of Form A and Form B of apremilast.

1277. An overlay of the synchrotron-XRPD pattern for the Form A reference powder, FGCB81, with Figure 1 in the '101 Patent demonstrates that the Form A reference powder is the same form of apremilast as Form A in the '101 Patent. Trial Tr. at 441:15–442:6 (Myerson Direct 6.16.21); PTX-1238 at PTX-1238_1–2.

1278. An overlay of the synchrotron-XRPD pattern for the Form B reference powder, FGCB54, with Figure 5 in the '101 Patent demonstrates that the Form B reference powder is the same form of apremilast as Form B in the '101 Patent. Trial Tr. at 442:7–16 (Myerson Direct 6.16.21); PTX-1238 at PTX-1238_5–6.

(3) Dr. Gozzo's testing of samples of exhibit batches of Zydus's API shows Form B is present in Zydus's API.

1279. Dr. Gozzo's synchrotron-XRPD data shows that every sample of all three exhibit batches of Zydus's API has a mixture of Form B and Form A of apremilast. Trial Tr. at 452:4–9 (Myerson Direct 6.16.21).

1280. Batches AEA1MSJ01D [FGCB79], AEA1MSJ02D [FGCB80], and AEA1MSJ03D [FGCB78] are exhibit batches of Zydus's API, which were manufactured according to Zydus's ANDA, are representative of the API in Zydus's ANDA Products, and were analyzed by Zydus according to its own specification and the results were submitted to FDA as part of Zydus's ANDA. JTX-900 at JTX-900_1; PTX-574 at PTX-574_116; PTX-573 at PTX-573_5, _15; s*ee also* Trial Tr. at 440:8–441:14 (Myerson Direct 6.16.21).

1281. Overlays of diffractograms comparing samples of Zydus's API to the Form A and Form B reference powders demonstrate that all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80] contain a mixture of Form A and Form B of apremilast. Trial Tr. at 442:17–443:15 (Myerson Direct 6.16.21); PTX-1238 at PTX-1238_18–35.

1282. XRPD peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta (within the acceptable error range of plus or minus 0.2 degrees 2-theta) were detected on the diffractogram and in the peak list for all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 442:17–446:6 (Myerson Direct 6.16.21).

1283. XRPD peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta are present in the diffractogram and peak lists for the Form B reference powder. PTX-1238 at PTX-1238_5–8; PTX-1241 at PTX-1241_1; Trial Tr. at 442:17–444:17 (Myerson Direct 6.16.21).

1284. Form B contributes to the intensity of the XRPD peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta in all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 442:17–446:6 (Myerson Direct 6.16.21).

1285. XRPD peaks at 10.1, 13.5, and 26.9 degrees 2-theta are also present in the Form A reference powder. PTX-1238 at PTX-1238_1–4; PTX-1241 at PTX-1241_12; Trial Tr. at 442:17–444:17 (Myerson Direct 6.16.21).

1286. Form A and Form B contribute to the intensity of the XRPD peaks at 10.1, 13.5, and 26.9 degrees 2-theta in all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 442:17–446:6 (Myerson Direct 6.16.21).

1287. Form B generates an XRPD peak at 20.7 degrees 2-theta; Form A does not generate an XRPD peak at 20.7 degrees 2-theta. PTX-1238 at PTX-1238_1–8; PTX-1241 at PTX-1241_1, _12; Trial Tr. at 442:17–444:17 (Myerson Direct 6.16.21).

1288. Form A does not contribute to the intensity of the XRPD peak at 20.7 degrees 2-theta in all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 442:17–446:6 (Myerson Direct 6.16.21).

1289. Form B contributes to the intensity of the XRPD Peak at 20.7 degrees 2-theta in all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 442:17–446:6 (Myerson Direct 6.16.21).

1290. XRPD peaks at 6.0, 10.7, 12.4, and 13.0 degrees 2-theta are generated by Form B, as evidenced by the XRPD diffractogram for Form B in the '101 Patent, as well as Dr. Gozzo's analysis of the Form B reference powder. Trial Tr. 447:10–448:10 (Myerson Direct); JTX-5 at JTX-5_9; *see also* PTX-1238 at PTX-1238_5–8; PTX-1241 at PTX-1241_1.

1291. XRPD peaks at 6.0, 10.7, 12.4, and 13.0 degrees 2-theta are not generated by Form A, as evidenced by the XRPD diffractogram for Form A in the '101 Patent, as well as Dr. Gozzo's analysis of the Form A reference powder. Trial Tr. at 447:10–448:10 (Myerson Direct 6.16.21); JTX-5 at JTX-5_5; *see also* PTX-1238 at PTX-1238_1–4; PTX-1241 at PTX-1241_12.

1292. XRPD peaks at 6.0, 10.7, 12.4, and 13.0 degrees 2-theta are not generated by Form F, as evidenced the XRPD diffractogram for Form F in the '101 Patent. Trial Tr. at 447:10–448:10 (Myerson Direct 6.16.21); JTX-5 at JTX-5_25.

1293. XRPD peaks at 6.0, 10.7, 12.4, and 13.0 degrees 2-theta are unique to Form B as compared to Forms A and F. Trial Tr. at 447:10–448:10 (Myerson Direct 6.16.21); JTX-5 at JTX-5_5, _9, _25; *see also* PTX-1238 at PTX-1238_1–8; PTX-1241 at PTX-1241_1, _12.

1294. An XRPD peak at 12.4 is a unique peak to Form B as compared to Forms A and F even though a reference standard of Form F was not analyzed by synchrotron-XRPD. Trial Tr. at 488:15–24 (Myerson Redirect 6.16.21).

1295. The other forms of apremilast mentioned in the '101 Patent in addition to Forms A, B, or F of apremilast (*i.e.*, Forms C, D., E, and G) cannot be present in Zydus's API because Forms C, D, E, and G are solvates that cannot be made using Zydus's API manufacturing process because they require solvents that are not used in Zydus's API manufacturing process. Trial Tr. at 448:11–22 (Myerson Direct 6.16.21).

1296. An XRPD peak at 12.4 degrees 2-theta (within the acceptable error range of plus or minus 0.2 degrees 2-theta) was detected on the diffractograms and in the peak lists for all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 449:10–450:9 (Myerson Direct 6.16.21).

1297. XRPD peaks at 6.0, 10.7, and 13.0 degrees 2-theta (within the acceptable error range of plus or minus 0.2 degrees 2-theta) were detected on the diffractograms and in the peak lists for all three samples of two exhibit batches of Zydus's API [FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 450:10–451:10 (Myerson Direct 6.16.21).

1298. The reason that the XRPD peaks at 6.0, 10.7, and 13.0 degrees 2-theta were not detected on the diffractograms and in the peak lists for the samples of the third exhibit batch of Zydus's API [FGCB78] (although they were detected in the samples of the other two exhibit batches of Zydus's API [FGCB79, FGCB80]) is because they were below the limit of detection.

Trial Tr. at 450:20–451:2 (Myerson Direct 6.16.21). In other words, the amount of Form B in those samples was below the level where those peaks could be detected.

1299. XRPD peaks at 6.0, 10.7, 12.4, 13.0, and 20.7 degrees 2-theta were not detected in Zydus's internal testing included with its ANDA because they were below the limit of detection for the laboratory-XRPD used for Zydus's internal testing. Trial Tr. at 448:23–449:9 (Myerson Direct 6.16.21). In other words, the amount of Form B in those samples was below the level where those peaks could be detected with the laboratory-XRPD used by Zydus.

1300. If Zydus had analyzed its own samples using synchrotron-XRPD, the level of detection would be lower, and thus the synchrotron analysis could have detected peaks in those samples that were not detected by Zydus's laboratory XRPD. Trial Tr. at 1267:22–1268:10 (Miller Cross 6.22.21).

1301. XRPD peaks at 15.7, 16.3, 18.1, 22.5, 24.7, 26.2, and 29.1 degrees 2-theta are also characteristic of Form B, as described in the '101 Patent. JTX-5 20:13–27; Trial Tr. at 451:3–452:3 (Myerson Direct 6.16.21).

1302. XRPD peaks at 15.7, 16.3, 18.1, 22.5, 24.7, 26.2, and 29.1 degrees 2-theta (within the acceptable error range of plus or minus 0.2 degrees 2-theta) were detected on the diffractograms and in the peak lists for all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. PTX-1241 at PTX-1241_6–11; PTX-1238 at PTX-1238_18–35; Trial Tr. at 451:3–452:3 (Myerson Direct 6.16.21).

1303. Zydus's expert, Dr. Miller, conceded that he cannot rule out the presence of Form B in the samples of Zydus's API analyzed by Dr. Gozzo. Trial Tr. at 1266:5–8 (Miller Cross 6.22.21).

1304. Dr. Gozzo's data confirms that all of the API batches analyzed by Dr. Gozzo passes Zydus's internal XRPD specification at the time she tested the batches because XRPD peaks at 7.9, 14.6, 17.2, 23.0, and 24.9 degrees 2-theta, plus or minus 0.2 degrees 2-theta, were

detected on the diffractograms and in the peak lists for all three samples of all three exhibit batches of Zydus's API [FGCB78, FGCB79, FGCB80]. *Compare* PTX-1241 at PTX-1241_6–11, *and* PTX-1238 at PTX-1238_18–35, *with* ZSF (A2) ¶ 20 (ECF No. 422), *and* PTX-573 at PTX-573_21.

b) The samples of Zydus's API tested by Dr. Gozzo were representative at the time they were tested of the API used to make Zydus's ANDA Products.

1305. Based on the length of time the samples of Zydus's API tested by Dr. Gozzo were stored and how they were stored, those samples were representative of the API used to make Zydus's ANDA Products at the time they tested. PF ¶¶ 1306–31.

(1) Zydus's exhibit batches, when tested by Dr. Gozzo, could have been used to make batches of Zydus's ANDA Products.

1306. The batches of Zydus's API tested by Dr. Gozzo could have been used to make batches of Zydus's ANDA Products at the time they were tested. PF ¶¶ 1307–19.

1307. Zydus's API has a retest date, not an expiration date, which means that API batches can be used to manufacture Zydus's ANDA Products as long as the API passes the retest specification. Trial Tr. at 452:10–453:9 (Myerson Direct 6.16.21).

1308. Zydus's API samples were tested by Dr. Gozzo 34 months after manufacture. Zydus's API passed retest specification 36 months after manufacture; that is, after Dr. Gozzo's testing. Trial Tr. at 452:10–453:9 (Myerson Direct 6.16.21).

1309. The chain of custody of samples of Zydus's API ensured proper handling prior to testing by Dr. Gozzo. Trial Tr. at 452:10–453:9 (Myerson Direct 6.16.21).

1310. Zydus's ANDA provides that Zydus's API has a retest period of six months. PTX-1309 at PTX-1309_1; Trial Tr. at 453:12–23 (Myerson Direct 6.16.21).

1311. Zydus's ANDA specifies that Zydus's API should be stored in tightly closed containers at temperatures below 25 degrees Celsius (which is approximately 77 degrees

Fahrenheit); there are no other storage requirements for Zydus's API. PTX-1309 at PTX-1309_1; Trial Tr. at 453:12–23 (Myerson Direct 6.16.21); Trial Tr. at 1260:16–1261:5 (Miller Cross 6.22.21).

1312. Zydus's ANDA includes long term stability studies up to 60 months after the manufacturing date of Zydus's API, indicating that Zydus's API may continue to be used to make ANDA Product batches at least up to 60 months after manufacture provided it continues to pass the API teste specification. PTX-1310 at PTX-1310_1; Trial Tr. at 453:24–454:12 (Myerson Direct 6.16.21).

1313. Zydus's own stability testing shows that Zydus's API batch number AEA1MSJ01D, which is one of the exhibit batches tested by Dr. Gozzo [FGCB79], passed Zydus's API retest specification 36 months after manufacture, which is two months after Dr. Gozzo conducted her testing of Zydus's API samples. PTX-1151 at PTX-1151_4; Trial Tr. at 454:13–455:25 (Myerson Direct 6.16.21); Trial Tr. at 486:7–20 (Myerson Redirect 6.16.21).

1314. Zydus's 36-month testing of batch number AEA1MSJ01D was conducted on samples that were stored in their container at 25 degrees Celsius and 60% relative humidity. PTX-1151 at PTX-1151_4; Trial Tr. at 455:3–12 (Myerson Direct 6.16.21).

1315. Guidances from FDA and ICH provide that if an API batch passes retest specification, then that API batch can be used to manufacture batches of an ANDA Product. Trial Tr. at 456:1–7 (Myerson Direct 6.16.21).

1316. Zydus's API batch number AEA1MSJ01D met the Zydus's API retest specification at 36-months in August 2020 and could have been used to manufacture ANDA Product batches at the time Dr. Gozzo tested samples of AEA1MSJ01D [FGCB79] 34 months after its manufacture date. Trial Tr. at 456:1–7 (Myerson Direct 6.16.21); PTX-1151_4.

1317. Zydus's own testing also demonstrates that AEA1ASJ01D, AEA1ASJ02D, and AEA1ASJ03D, which are unmicronized versions of the three exhibit batches tested by Dr.

Gozzo, passed Zydus's retest specification after 36 months in August 2020, which indicates that batch numbers AEA1MSJ01D [FGCB79], AEA1MSJ02D [FGCB80], and AEA1MSJ03D [FGCB78] could have been used to manufacture ANDA Product batches at the time Dr. Gozzo tested them 34 months after their manufacture date. *See* PTX-1151 at PTX-1151_1–3.

1318. Dr. Miller did not dispute that FDA and ICH guidelines permit an API batch to be used to manufacture ANDA Products as long as the API batch passes its specification upon retesting.

1319. Dr. Miller did not dispute that the batches in Zydus's possession passed Zydus's internal specification at 36 months or that Zydus could have manufactured ANDA Product batches from those API batches at 36 months.

(2) The samples of Zydus's exhibit batches that were tested by Dr. Gozzo were stored consistent with Zydus's storage requirement prior to testing.

1320. The samples of Zydus's API that were tested by Dr. Gozzo are representative that of the API that will be used to manufacture Zydus's ANDA Products. Trial Tr. at 457:6–10 (Myerson Direct 6.16.21).

1321. The chain of custody for the samples of Zydus's API that were analyzed by Dr. Gozzo shows that the samples were always kept in their original packaging; they were stored in climate-controlled environments in air-conditioned offices at law firms or private residences; they were shipped under proper temperature control to Switzerland; and then Dr. Gozzo stored and prepared the samples at appropriate conditions. Trial Tr. at 456:11–457:2 (Myerson Direct 6.16.21); PTX-1115; PTX-1246; PTX-1247; PTX-1254; PTX-1255.

1322. There is no evidence that the samples of Zydus's API were ever exposed to temperatures greater than 25 degrees Celsius prior to analysis by Dr. Gozzo. Trial Tr. at 485:8–22 (Myerson Redirect 6.16.21); Trial Tr. at 1261:6–12 (Miller Cross 6.22.21).

1323. Even if the samples tested by Dr. Gozzo had been exposed to minor temperature excursion beyond 25 degrees Celsius prior to analysis by Dr. Gozzo, that exposure would not affect the form of apremilast in Zydus's API because any such exposure is not a mechanism to change the polymorphs present in Zydus's API, including Form A to Form B. Trial Tr. at 485:23–486:6 (Myerson Redirect 6.16.21).

1324. The way that the samples of Zydus's API tested by Dr. Gozzo were handled would not affect the crystalline forms present, including the crystalline composition as between Forms A, B and F of apremilast. Trial Tr. at 486:21–487:1 (Myerson Redirect 6.16.21).

1325. Zydus's expert, Dr. Steven Miller, is not an expert in pharmaceutical handling, pharmaceutical storage, pharmaceutical packaging, or crystallization. Thus, Dr. Miller, is not qualified to opine on issues related to pharmaceutical handling, pharmaceutical storage, pharmaceutical packaging, or crystallization, including whether conversion could or would occur between Form A and Form B. Trial Tr. at 1258:17–1260:8, 1262:24–1263:24 (Miller Cross 6.22.21). Dr. Miller conceded that he could not identify any conditions under which Form A could or would convert to Form B. Trial Tr. at 1263:5–24 (Miller Cross 6.22.21).

1326. The samples of Zydus's API that were tested by Dr. Gozzo were shipped at controlled temperature, in between 15 and 25 degrees Celsius, in packaging monitored by a temperature logger included in the parcel. Trial Tr. at 497:22–498:13 (Gozzo Direct 6.16.21); PTX-1242 through PTX-1251.

1327. After receipt, Dr. Gozzo stored the samples of Zydus's API that she analyzed, from the time of receipt until the time of analysis, at 22 degrees Celsius plus/minus 2 degrees Celsius. Trial Tr. at 497:22–498:13, 501:3–502:6 (Gozzo Direct 6.16.21); PTX-1246; PTX-1247; PTX-1254.

1328. All samples of Zydus's API that were tested by Dr. Gozzo were received in their original sealed packages from Zydus, which were, for the API, sealed aluminum foil packets

that protect from light and moisture. Trial Tr. at 497:22–498:13 (Gozzo Direct 6.16.21); PTX-1247; Trial Tr. at 1261:19–1262:4 (Miller Cross 6.22.21).

1329. There was no damage to the packaging of any of samples of Zydus API prior to receipt by Dr. Gozzo. Trial Tr. at 498:14–500:18 (Gozzo Direct 6.16.21); PTX-1247; PTX-1254.

1330. All samples of Zydus's API were prepared shortly before the synchrotron testing and were all prepared under controlled conditions of temperature, which is 22 degrees Celsius plus/minus 2 degrees Celsius, and under nitrogen atmosphere and controlled relative humidity. Trial Tr. at 501:3–502:6 (Gozzo Direct 6.16.21); PTX-1246; PTX-1247; PTX-1254.

1331. Dr. Gozzo's receipt, handling, storage, and preparation of Zydus's API was in accordance with her standard practice. Trial Tr. at 502:5–10 (Gozzo Direct 6.16.21).

c) Zydus's ANDA Products will contain Form B because Zydus's API contains Form B.

(1) Zydus's ANDA Products are manufactured using Zydus's API, which contains Form B.

1332. Zydus's ANDA Products for which it seeks FDA approval to market and sell will contain Form B of apremilast. PF ¶¶ 1333–36.

1333. Zydus's API is used to manufacture Zydus's ANDA Products. PF ¶¶ 1239–47, 1347–50.

1334. Zydus represented to FDA in its ANDA that the polymorphic form its API does not change when manufactured into Zydus's ANDA Product and stored. *E.g.*, JTX-901 at JTX-901_3, _12 ("it is concluded that the polymorphic form of the drug substance (apremilast) in the drug product (apremilast tablets) remains unchanged after manufacturing of the drug product and upon storage.").

1335. Zydus's API contains Form B. PF ¶¶ 1264–1331.

1336. If Form B is present in Zydus's API, then it will be present in Zydus's ANDA Products because there is no mechanism to change the crystalline form once it is in the ANDA Product. Trial Tr. at 463:6–11 (Myerson Direct 6.16.2021).

(2) Independent testing of Zydus's ANDA Product is consistent with the presence of Form B.

1337. Synchrotron-XRPD testing on samples of Zydus's ANDA Products by Dr. Gozzo is consistent with the presence of Form B. PF ¶¶ 1338–56.

(a) Overview of Dr. Gozzo's testing

1338. Zydus produced samples of Zydus ANDA Product Batch Nos. EE70341 (10mg), EE70342 (10mg), EE70343 (10mg), EE70349 (20mg), EE70350 (20mg), EE70351 (20mg), EE70360 (30mg), EE70361 (30mg), and EE70362 (30mg) to Covington & Burling LLP. PTX-1115 at PTX-1115_1–3 at ¶¶ 2, 4, 5.

1339. Dr. Gozzo received samples of Zydus ANDA Product Batch Nos. EE70341 (10mg), EE70342 (10mg), EE70343 (10mg), EE70349 (20mg), EE70350 (20mg), EE70351 (20mg), EE70360 (30mg), EE70361 (30mg), and EE70362 (30mg) from Covington and Burling. PTX-1246; PTX-1247; PTX-1253 PTX-1254; *see also* PTX-1115 at PTX-1115_3–4 at ¶ 6.

1340. Dr. Fabia Gozzo performed independent testing on samples of Zydus's ANDA Products by synchrotron-XRPD in June 2020. Trial Tr. at 458:15–459:5 (Myerson Direct 6.16.21); Trial Tr. at 496:22–497:17 (Gozzo Direct 6.16.21); *see also* Trial Tr. at 1229:24–25 (Miller Direct 6.22.21); PTX-1254.

1341. The additional samples that Dr. Gozzo prepared and analyzed by synchrotron-XRPD analysis as part of her analysis of samples of Zydus's ANDA Products are listed in Table 4 below.

Table 4 - Zydus's ANDA Products—Sample Description

ESS ID Code	Description	Sample Characteristics
FGCB70	Low-Substituted Hydroxypropyl Cellulose LHPC Grade LH-21 from Shin-Etsu with Batch/Lot No: 9011035	1 capillary
FGCB71	Magnesium Stearate Ligamed MF-2-V from Peter Greven with Batch/Lot No: C944017	1 capillary
FGCB72	Microcrystalline Cellulose Avicel PH102 from FMC with Batch/Lot No: 71731c	1 capillary
FGCB73	Kollidon VA64 Copovidone from BASF with Batch/Lot No: 36557247G0	1 capillary
FGCB74	Colloidal Silicon Dioxide Aerosil 200 Pharma from Evonik with Batch/Lot No: 158091814	1 capillary
FGCB75	Zydus Apremilast 30 mg Tablet Drug Product in bottle with Batch No: EE70362 (ZYDAPR0019058)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB76	Zydus Apremilast 30 mg Tablet Drug Product in bottle with Batch No: EE70361 (ZYDAPR0019057)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB77	Zydus Apremilast 30 mg Tablet Drug Product in bottle with Batch No: EE70360 (ZYDAPR0019056)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB82	Zydus Apremilast 10 mg Tablet Drug Product in blister with Batch No: EE70341 (ZYDAPR0019092)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB83	Zydus Apremilast 20 mg Tablet Drug Product in blister with Batch No: EE70350 (ZYDAPR0022530)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB84	Zydus Apremilast 20 mg Tablet Drug Product in blister with Batch No: EE70351 (ZYDAPR0022540)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB85	Zydus Apremilast 20 mg Tablet Drug Product in blister with Batch No: EE70349 (ZYDAPR0019072)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2

FGCB86	Zydus Apremilast 10 mg Tablet Drug Product in blister with Batch No: EE70343 (ZYDAPR0022516)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2
FGCB87	Zydus Apremilast 10 mg Tablet Drug Product in blister with Batch No: EE70342 (ZYDAPR0022505)	1 integer tablet: TAB 2 capillaries: CAP1, CAP2

ZSF (A2) ¶ 21 (ECF No. 422); *see also* PTX-1253; Trial Tr. at 458:15–459:5 (Myerson Direct 6.16.21); Trial Tr. 508:11–15, 509:10–510:9 (Gozzo Direct 6.16.21).

1342. Dr. Gozzo analyzed one intact tablet and two powderized tablet samples from each of the nine exhibit batches of Zydus's ANDA Products [FGCB75–77, FGCB82–87, each with Tab, Cap1, and Cap2] by synchrotron-XRPD, and created diffractograms and peak lists for each. Trial Tr. at 508:11–15, 509:10–510:9 (Gozzo Direct 6.16.21); PTX-1239 at PTX-1239_8–43, _84–155; PTX-1241 at PTX-1241_3–5, _13–18.

1343. Dr. Gozzo analyzed one sample from each of the five excipients used in Zydus's ANDA Products [FGCB70–74] by synchrotron-XRPD and created diffractograms and peak lists for each. Trial Tr. at 508:11–15, 509:10–510:9 (Gozzo Direct 6.16.21); PTX-1239 at PTX-1239_3–7; PTX-1241 at PTX-1241_2.

1344. Dr. Gozzo created an overlay of the experimental synchrotron-diffractograms comparing the three samples from each of the nine Exhibit Batches of Zydus's ANDA Products [FGCB75–77, FGCB82–87, each with Tab, Cap1, and Cap2] to the experimental synchrotron-diffractograms for the five excipients, one batch of Zydus's API, and the Form A and Form B reference powders. Trial Tr. at 510:10–511:6 (Gozzo Direct 6.16.21); PTX-1238 at PTX-1238_36–53.

1345. Dr. Gozzo created a peak list for each sample analyzed by synchrotron-XRPD using TOPAS software, followed by a visual analysis to verify that every peak in the peak list corresponds to a peak in the synchrotron-diffraction pattern. Trial Tr. at 504:22–505:22 (Gozzo Direct 6.16.21).

1346. Dr. Gozzo's tests, methodologies, and procedures were appropriate. Trial Tr. 440:20–25 at (Myerson Direct 6.16.21).

1347. Batches EE70341 (10mg), EE70342 (10mg), EE70343 (10mg), EE70349 (20mg), EE70350 (20mg), EE70351 (20mg), EE70360 (30mg), EE70361 (30mg), and EE70362 (30mg) are exhibit batches of Zydus's ANDA Products, which were manufactured according to Zydus's ANDA, are representative of Zydus's ANDA Products, and were analyzed by Zydus according to its own specification and the results were submitted to FDA as part of Zydus's ANDA. PTX-574 at PTX-574_116; *see also* Trial Tr. at 458:15–459:5 (Myerson Direct 6.16.21); PTX-574 at PTX-574_51–64; JTX-900 at JTX-900_1; PTX-573 at PTX-573_5, _15.

1348. The following batches of Zydus's ANDA Products were made from batch No. AEA1MSJ01D of Zydus's API [FGCB79]: EE70341 (10mg) [FGCB82], EE70349 (20mg) [FGCB85], and EE70360 (30mg) [FGCB77]. PTX-574 at PTX-574_116; *see also* Trial Tr. 458:15–459:5 at (Myerson Direct 6.16.21).

1349. The following batches of Zydus's ANDA Products were made from batch No. AEA1MSJ02D of Zydus's API [FGCB80]: EE70342 (10mg) [FGCB87] and EE70343 (10mg) [FGCB86], EE70350 (20mg) [FGCB83] and EE70351 (20mg) [FGCB84], and EE70361 (30mg) [FGCB76] and EE70362 (30mg) [FGCB75]. PTX-574 at PTX-574_116; *see also* Trial Tr. at 458:15–459:5 (Myerson Direct 6.16.21).

1350. The following batches of Zydus's ANDA Products were made from batch No. AEA1MSJ03D of Zydus's API [FGCB78]: EE70343 (10mg) [FGCB86], EE70351 (20mg) [FGCB84], and EE70362 (30mg) [FGCB75]. PTX-574 at PTX-574_116; *see also* Trial Tr. at 458:15–459:5 (Myerson Direct 6.16.21).

(b) Dr. Gozzo's testing of samples of Exhibit Batches of Zydus's ANDA Products is consistent with the presence of Form B.

1351. Zydus's ANDA product is made up of a number of excipients plus the active ingredient, which is apremilast; Zydus's ANDA Products are 8.67% by weight API, which is a relatively small percentage. Trial Tr. at 459:15–460:11 (Myerson Direct 6.16.21); PTX-576 at PTX-576_8.

1352. While Dr. Gozzo tested samples of Zydus's ANDA Products after their proposed 24-month expiration date, the API in Zydus's ANDA Products would still have been within specification. In fact, samples from the very same batches passed their retest specification, 36 months after manufacture. Trial Tr. at 459:6–14 (Myerson Direct 6.16.21).

1353. XRPD Peaks at 10.1, 13.5, and 26.9 degrees 2-theta (within the acceptable error range of plus or minus 0.2 degrees 2-theta) were detected on the diffractogram and in the peak list for every sample of every exhibit batch of Zydus's ANDA Products [FGCB75–77, FGCB82–87], which is consistent with the presence of Form B tablets containing the 8.67 percentage by weight of the API in the tablets. Trial Tr. at 460:12–461:11 (Myerson Direct 6.16.21); PTX-1241 at PTX-1241_3–5, 13–18; PTX-1238 at PTX-1238_36–53; PTX-1239; PTX-576 at PTX-576_8.

1354. The relatively small percentage of API in Zydus's ANDA Products (8.67% by weight) means that when analyzing Zydus's ANDA Products by XRPD, it will be difficult to see peaks that are generated by apremilast, including Form B, because of the presence of relatively large quantities of excipients. Trial Tr. at 460:6–11 (Myerson Direct 6.16.21).

1355. A peak at 20.7 degrees 2-theta (within the acceptable error range of plus or minus 0.2 degrees 2-theta) is present (but is below the limit of detection, based on the API diffractograms and peak lists), in every sample of every exhibit batch of Zydus's ANDA Products [FGCB75–77, FGCB82–87], which is consistent with the presence of Form B in

tablets containing the 8.67 percentage by weight of the API in the tablets. Trial Tr. 460:12–461:11 at (Myerson Direct 6.16.21); Trial Tr. 487:2–488:8 at (Myerson Redirect 6.16.21); PTX-1241 at PTX-1241_3–5, _13–18; PTX-1238 at PTX-1238_36–53; PTX-1239; PTX-576 at PTX-576_8.

1356. The data generated from Dr. Gozzo's testing of samples of the Exhibit Batches of Zydus's ANDA Product is consistent with the presence of Form B. Trial Tr. at 461:12–16 (Myerson Direct 6.16.21).

(3) Zydus's API and ANDA specifications permit the presence of Form B.

1357. Zydus's API and ANDA Specifications determine what Zydus will manufacture and sell, if Zydus's ANDA obtains final approval from FDA. Trial Tr. at 461:17–462:3 (Myerson Direct 6.16.21); *see also id.* at 462:4–15.

1358. Zydus's ANDA controls certain aspects of the API through a "drug substance specification at release and stability," which includes a "test for polymorphism by XRD." ZSF (A2) ¶ 21 (ECF No. 422).

1359. Zydus's XRPD specification for its API (Active Pharmaceutical Ingredient, also known as "drug substance") states: "It should exhibits [sic] characteristic 2θ peaks at 7.9º, 14.6º, 17.2º, 23.0º, and 24.9º±0.2º." ZSF (A2) ¶ 20 (ECF No. 422); PTX-573 at PTX-573_21; Trial Tr. at 462:4–18 (Myerson Direct 6.16.21).

1360. Zydus's XRPD specification for its API tests for the presence of five XRPD peaks associated with Form A; it does not test for the presence or absence of any other peak, including peaks that are unique to Form B of apremilast. Trial Tr. at 462:4–463:1 (Myerson Direct 6.16.21); PTX-573 at PTX-573_21.

1361. A sample of Zydus's API that contains a mixture of Form A and Form B would meet the specification for Zydus's API. Trial Tr. at 462:9–15, 462:23–463:5 (Myerson Direct 6.16.21); *see also* PTX-573 at PTX-573_21.

1362. Zydus's specification for its ANDA Products does not test for polymorphism or XRPD. Trial Tr. at 462:19–463:1 (Myerson Direct 6.16.21); PTX-577.

1363. A sample of Zydus's ANDA Products that contains a mixture of Form A and Form B would meet the specification for Zydus's ANDA Products. Trial Tr. at 462:19–463:5 (Myerson Direct 6.16.21); *see also* PTX-577.

6. Summary: Zydus infringes claims 1 and 15 of the '101 Patent

1364. Zydus's API meets every limitation of claim 1 of the '101 Patent. Trial Tr. at 463:12–23 (Myerson Direct 6.16.21).

1365. If Form B is present in a batch of Zydus's API, Form B will be present in batches of Zydus's ANDA Products made from that batch of Zydus's API because there is no mechanism to change the crystalline form of Zydus's API once it is in Zydus's ANDA Products. Trial Tr. at 463:6–11 (Myerson Direct 6.16.21).

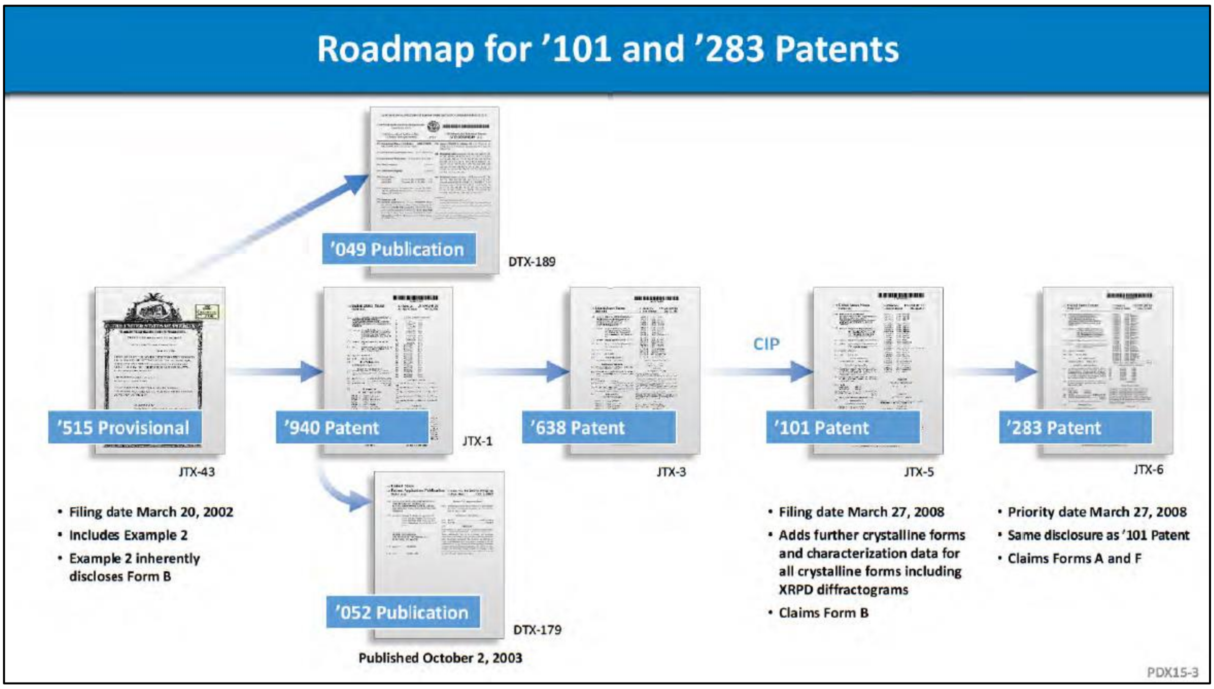
1366. Zydus's ANDA Products meet every limitation of claims 1 and 15 of the '101 Patent. Trial Tr. at 463:12–23 (Myerson Direct 6.16.21).

E. Defendants Have Failed to Prove by Clear and Convincing Evidence that Claims 1 and 15 of the '101 Form B Patent Are Invalid.

1367. Defendants have failed to prove by clear and convincing evidence that claims 1 and 15 of the '101 Patent are invalid for obviousness. The only combinations of references on which Dr. Steed offered obviousness opinions are (1) the '052 Publication and the "Knowledge of a POSA," and (2) the '052 Publication in combination with Brittain 1997, ICH Guidelines, Guillory, Brittain 1999, and the "Knowledge of a POSA," both of which rely on the '052 Publication. Trial Tr. at 1125:15–1126:4 (Steed Direct 6.22.21). The '049 Publication, which has the same disclosures as the '052 Publication including Example 2, *see* PF ¶ 1375, was cited on the fact of the '101 Patent and '283 Patent and considered by the USPTO during prosecution of both patents. JTX-5 at JTX-5_3, [56]; JTX-6 at JTX-6_3 [56].

1368. The ’052 Publication was published on October 2, 2003. DTX-179 at DTX-179_1; *see also* Trial Tr. at 1591:18–1592:23 (Myerson Direct 6.24.21).

1369. The ’101 Patent issued from a continuation-in-part application filed on March 27, 2008 that claims priority to the ’515 Provisional. The ’515 Provisional is correctly cited on the face of the ’101 Patent and on every patent in the chain from the ’515 Provisional to the ’101 Patent: the ’940 Patent and the ’638 Patent. JTX-5 at JTX-5_2 at [60]; JTX-1 at JTX-1_2 at [60]; JTX-3 at JTX-3_2 at [60] *see also* Trial Tr. at 1572:23–1574:18 (Myerson Direct 6.24.21) (referencing PDX15-3).



1370. The ’515 Provisional was filed on March 20, 2002. *E.g.*, JTX-43 at JTX-43_2; JTX-5 at JTX-5_2 at [60]; *see also* Trial Tr. at 1572:23–1574:18 (Myerson Direct 6.24.21) (referencing PDX15-3); Trial Tr. at 1081:8–12 (Steed Direct 6.22.21).

1371. The ’052 Publication is not prior art to claims 1 and 15 of the ’101 Patent if those claims are entitled to the benefit of the filing date of the ’515 Provisional. Trial Tr. at 1591:18–1592:23 (Myerson Direct 6.24.21); Trial Tr. at 1130:17–1131:10 (Steed Cross 6.22.21).

1. Claims 1 and 15 of the '101 Form B Patent are entitled to a March 20, 2002 priority date because Example 2 of the '515 Provisional provides written description support for claims 1 and 15 and enables a POSA to practice claims 1 and 15 without undue experimentation.

a) The first application leading to the '101 Form B Patent, the '515 Provisional, describes making a solid crystalline form of apremilast.

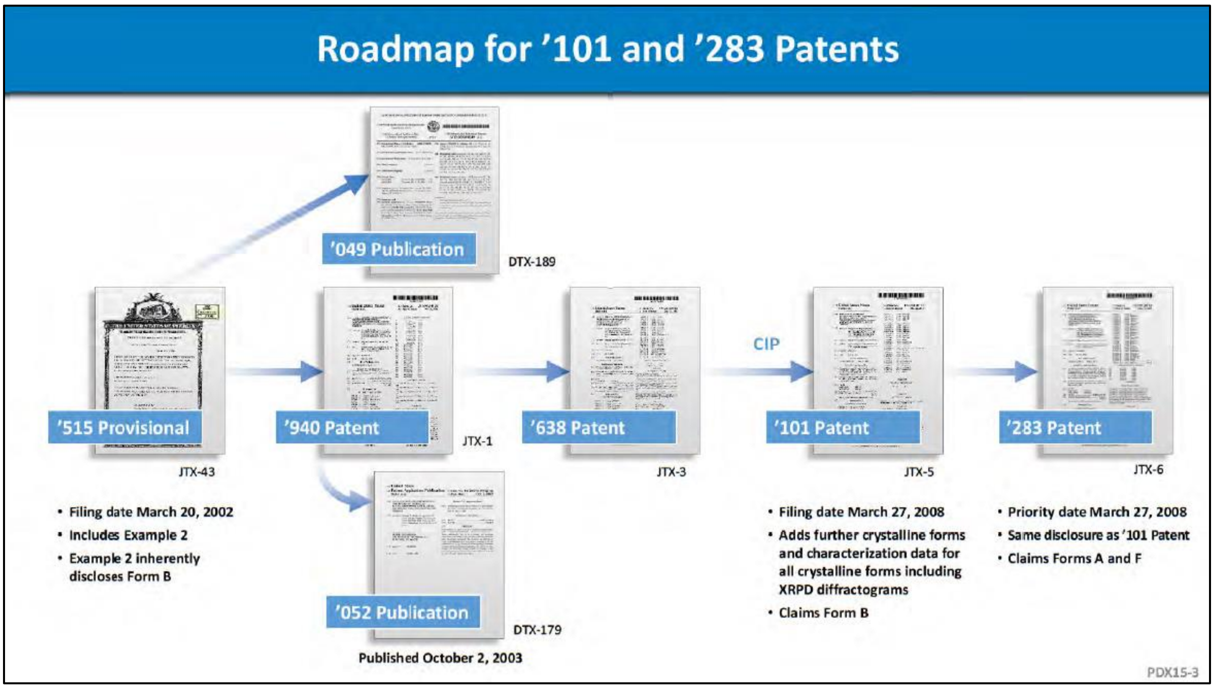
1372. Example 2 in the '515 Provisional is a synthetic chemical procedure for preparing apremilast (referred to as "Compound A" in the specification). Trial Tr. at 1576:15–1577:1 (Myerson Direct 6.24.21); Trial Tr. at 1087:25–1088:7 (Steed Direct 6.22.21); *see also, e.g.*, JTX-43 at JTX-43_29–30. Considering Example 2 to be a recipe for making apremilast is a good analogy. Trial Tr. at 1576:15–20 (Myerson Direct 6.24.21).

1373. The final step of Example 2 is a recrystallization of the synthesized apremilast from a binary solvent containing a 2:1 ratio of ethanol to acetone that results in a solid. Trial Tr. at 1576:15–1577:1 (Myerson Direct 6.24.21); *see also, e.g.*, JTX-43 at JTX-43_29–30. The result of Example 2 is solid apremilast). Trial Tr. at 1572:23–1573:1 (Myerson Direct 6.24.21).

1374. The recrystallization step of Example 2 uses a starting material having 98% ee. *E.g.*, Trial Tr. at 1578:21–1579:8 (Myerson Direct 6.24.21); JTX-43 at JTX-43_29–30. "ee" means enantiomeric excess, which is a measure of the purity of one enantiomer of a compound as compared to the other enantiomer of the compound. Trial Tr. at 1579:23–1580:8 (Myerson Direct 6.24.21).

1375. Example 2 is word for word the same in the '049 Publication, the '052 Publication, the patents and applications leading to the '101 Patent, namely, the '515 Provisional, the '940 Patent, and the '638 Patent, as well as in the '101 Patent and the '283 Patent. Trial Tr. at 1573:5–11 (Myerson Direct 6.24.21) (discussing PDX15-3); Trial Tr. at 1131:15–1132:8 (Steed Cross 6.22.21); *see also, e.g.*, JTX-43 at JTX-43_28–30; DTX-189 at

DTX-189_28–30; DTX-179 at DTX-179_15; JTX-1 at 21:8–22:59; JTX-3 at 21:6–22:29; JTX-5 at 39:30–40:57; JTX-6 at 39:17–40:46.



1376. Example 2 does not name the solid form of apremilast that is produced when a POSA follows the example. Trial Tr. at 1573:2–4 (Myerson Direct 6.24.21).

1377. The '515 Provisional does not state that apremilast is polymorphic. *See* JTX-43. It would not have been known that apremilast was polymorphic until a second crystalline form was created, and there would have been no reason to name the crystalline form (e.g., Form B) until more than one crystalline form had been created. Trial Tr. at 1154:18–155:1 (Steed Cross 6.22.21).

1378. In the continuation-in-part application that issued as the '101 Patent, the patentees added information relating to different polymorphs of apremilast. They disclosed Form A, and C-G of apremilast for the first time, named Forms A-G for the first time, added analytical data related to Forms A-G of apremilast, and added information relating to making Forms A-G. Trial Tr. at 1573:12–1574:15 (Myerson Direct 6.24.21).

1379. Example 2 results in a crystalline form of apremilast. Trial Tr. at 1577:2–21 (Myerson Direct 6.24.21); Trial Tr. at 1194:2–5 (Sacchetti Cross 6.22.21).

b) Example 2 of the '515 Provisional inherently results in Form B of apremilast.

1380. Example 2 inherently discloses Form B of apremilast. Trial Tr. at 1571:23–1572:9 (Myerson Direct 6.24.21).

1381. When practiced by a POSA, Example 2 of the '515 Provisional inherently results in Form B of apremilast. PF ¶¶ 1382–1412.

1382. Every experiment in the record that faithfully replicated Example 2 resulted in Form B. PF ¶¶ 1383–1412.

1383. Teva, Zentiva, and Lek submitted a total of 13 experiments to the European Patent Office ("EPO") as part of an opposition proceeding to European Patent No EP-B-2276483. Trial Tr. at 1577:25–1578:17 (Myerson Direct 6.24.21); JTX-225 at JTX-225_1–2.

1384. Teva's experiments were a faithful replication of Example 2 based on a comparison of Teva's experimental procedure to Example 2. Each of Teva's experiment used a solvent system that was a 2:1 ratio of ethanol to acetone. Trial Tr. at 1578:18–1579:19 (Myerson Direct 6.24.21); JTX-43 at JTX-43_29; JTX-225 at JTX-225_39; *see also* Trial Tr. at 1144:4–19 (Steed Cross 6.22.21).

1385. Teva created four replications of Example 2, each of which resulted in Form B of apremilast as determined by XRPD analysis. Trial Tr. at 1579:20–22, 1580:9–22 (Myerson Direct 6.24.21); Trial Tr. at 1143:13–15, 1145:7–12 (Steed Cross 6.22.21); Trial Tr. at 1201:6–9 (Sacchetti Cross 6.22.21); JTX-225 at JTX-225_36, _46.

1386. Teva's experimental conditions replicating Example 2 covered different variations a POSA may have used in carrying out Example 2. JTX-225 at JTX-225_15 ("[T]he experimental data supplied by [Teva, Zentiva, and Lek] seem to be straight forward possibilities for the skilled person having the information disclosed in [Example 2] within the reasonable variations possible."); JTX-225 at JTX-225_17 ("[T]he experiments done by [Teva, Zentiva, and Lek] deem to be straight forward option for a chemist having the information of

[Example 2] in hands" and varied "different parameters like solvent purity, temperature, rate of cooling and duration of crystal formation."); Trial Tr. at 1580:13–22 (Myerson Direct 6.24.21).

1387. Teva's replications demonstrate that when Example 2 is performed, using the 2:1 ratio of ethanol to acetone set forth in Example 2, with both fast cooling and slow cooling, it generates From B of apremilast. Two of Teva's four replications of Example 2 were performed using fast cooling, both of which resulted in Form B. Trial Tr. at 1580:9–22 (Myerson Direct 6.24.21); JTX-225 at JTX-225_13–14, _39–41, _46; *see also* Trial Tr. at 1201:14–18 (Sacchetti Cross 6.22.21).

1388. Zentiva's experiment was a faithful replication of Example 2 based on a comparison of Zentiva's experimental procedure to Example 2. Zentiva's experiment used a solvent system that was a 2:1 ratio of ethanol to acetone. Trial Tr. at 1580:23–1581:15 (Myerson Direct 6.24.21); JTX-43 at JTX-43_29; JTX-225 at JTX-225_52; *see also* Trial Tr. at 1144:4–19 (Steed Cross 6.22.21).

1389. Zentiva's replication of Example 2 resulted in Form B of apremilast as determined by XRPD analysis. Trial Tr. at 1581:16–1582:3 (Myerson Direct 6.24.21); 1143:13–15, 1145:7–12 (Steed Cross 6.22.21); 1201:6–9 (Sacchetti Cross 6.22.21); JTX-225 at JTX-225_352–53.

1390. Zentiva's experimental conditions replicating Example 2 covered conditions a POSA may have used in carrying out Example 2. JTX-225 at JTX-225_15 ("[T]he experimental data supplied by [Teva, Zentiva, and Lek] seem to be straight forward possibilities for the skilled person having the information disclosed in [Example 2] within the reasonable variations possible."); JTX-225 at JTX-225_17 ("[T]he experiments done by [Teva, Zentiva, and Lek] deem to be straight forward option for a chemist having the information of [Example 2] in hands" and varied "different parameters like solvent purity, temperature, rate

of cooling and duration of crystal formation."); Trial Tr. at 1581:21–1582:3 (Myerson Direct 6.24.21).

1391. Zentiva's replications demonstrate that when Example 2 is performed, using the 2:1 ratio of ethanol to acetone set forth in Example 2, with fast cooling, it generates From B of apremilast. Zentiva's replication of Example 2 was performed using fast cooling (according to Dr. Sacchetti's definition of fast cooling), which resulted in Form B. Trial Tr. at 1581:16–1582:3 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14, _53; *see also* Trial Tr. at 1201:14–18 (Sacchetti Cross 6.22.21).

1392. Lek's experiments were a faithful replication of Example 2 as demonstrated by comparing Lek's experimental procedure to Example 2. Each of Lek's experiment used a solvent system that was a 2:1 ratio of ethanol to acetone. Trial Tr. at 1582:4–1583:24 (Myerson Direct 6.24.21); JTX-43 at JTX-43_29; JTX-225 at JTX-225_65; *see also* Trial Tr. at 1144:4–19 (Steed Cross 6.22.21).

1393. Lek is a subsidiary of Sandoz. JTX-225 at JTX-225_64.

1394. Lek created eight replications of Example 2, all of which resulted in Form B of apremilast as determined by XRPD analysis. Trial Tr. at 1583:14–24 (Myerson Direct 6.24.21); Trial Tr. at 1143:13–15, 1145:7–12 (Steed Cross 6.22.21); Trial Tr. at 1201:6–9 (Sacchetti Cross 6.22.21); JTX-225 at JTX-225_64, _66.

1395. Lek's experimental conditions replicating Example 2 covered different variations a POSA may have used in carrying out Example 2. JTX-225 at JTX-225_15 ("[T]he experimental data supplied by [Teva, Zentiva, and Lek] seem to be straight forward possibilities for the skilled person having the information disclosed in [Example 2] within the reasonable variations possible."); JTX-225 at JTX-225_17 ("[T]he experiments done by [Teva, Zentiva, and Lek] deem to be straight forward option for a chemist having the information of [Example 2] in hands" and varied "different parameters like solvent purity, temperature, rate

of cooling and duration of crystal formation."); Trial Tr. at 1583:14–24 (Myerson Direct 6.24.21).

1396. Lek's replications demonstrate that when Example 2 is performed, using the 2:1 ratio of ethanol to acetone set forth in Example 2, with both fast cooling and slow cooling, it generates From B of apremilast. Four of Lek's eight replications of Example 2 were performed using fast cooling, both of which resulted in Form B. Trial Tr. at 1583:14–24 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14, _66; *see also* Trial Tr. at 1201:14–18, 1201:25–1202:5 (Sacchetti Cross 6.22.21).

1397. The EPO data submitted by Teva, Zentiva, and Lek demonstrates that crystalline form of apremilast obtained when a POSA practices Example 2 always results in Form B. Trial Tr. at 1587:13–24 (Myerson Direct 6.24.21).

1398. While Celgene also submitted the results of an attempt to replicate Example 2 to the EPO as part of opposition proceeding to European Patent No EP-B-2276483, that experiment did not properly replicate Example 2. Trial Tr. at 1584:4–7 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14–15.

1399. Celgene's experiments deviated from the requirements of Example 2 by using a starting material having 100% ee instead of 98% ee as required by Example 2 and thus were not faithful replications of Example 2. Trial Tr. at 1584:10–16 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14–15.

1400. The European Patent Office stated that Celgene's use of a 100% ee starting material "will influence the outcome of crystallization" and "purity of an API used in recrystallization may have an impact on the outcome of recrystallization." Trial Tr. at 1584:4–16 (Myerson Direct 6.24.21); JTX-225 at JTX-225_15; *see also* Trial Tr. at 1145:21–1147:11 (Steed Cross 6.22.21).

1401. The purity of a starting material can have a meaningful influence on crystallization and the polymorphic outcome of the crystallization. Trial Tr. at 1584:18–1586:5 (Myerson Direct 6.24.21); DTX-125 at DTX-125_22 ("The presence of impurities can have a profound effect on the growth of crystals . . . . Some impurities can exert an influence at very low concentrations (less than one part per million)."); *see also* Trial Tr. at 1611:7–19 (Myerson Direct 6.24.21) (explaining that a new polymorph of ritonavir was unexpectedly discovered due to small change in the impurity profile of the starting material in the crystallization manufacturing process).

1402. The difference between 98% ee and 100% ee is 1% enantiomeric purity, which is a 10,000 parts per million difference. Trial Tr. at 1584:10–16, 1584:21–1585:2, 1586:3–5 (Myerson Direct 6.24.21).

1403. Celgene's experiments used continuous scratching over five hours, which is not a procedure that a POSA would have used. Continuous scratching means that the scientist was taking a rod and putting it inside the crystallization vessel and rubbing the side of the inside to help induce crystallization for five hours, which is not a typical thing a POSA would do. Trial Tr. at 1584:21–1585:10 (Myerson Direct 6.24.21).

1404. The results Celgene reported for its experiment indicate that it made a mistake in conducting the experiment or analyzing the results. Celgene represented to the EPO that it obtained Form C from its experiments. Trial Tr. at 1586:9–1587:10 (Myerson Direct 6.24.21); JTX-225 at JTX-225_15.

1405. Form C is a crystalline form of apremilast described in the '101 Patent that is a toluene solvate, which means that it contains toluene as part of the crystalline structure. A solvate like Form C cannot be made unless the solvent, here toluene, is present as part of the experiment. Trial Tr. at 1586:9–1587:10 (Myerson Direct 6.24.21); JTX-5 at 21:66–22:3.

1406. Toluene is not part of Example 2 and therefore cannot be part of any crystalline apremilast that is created from a faithful replication of Example 2. *E.g.*, JTX-43 at JTX-43_29; Trial Tr. at 1586:18–1587:10 (Myerson Direct 6.24.21).

1407. Celgene is either mistaken that it obtained Form C, or mistakenly deviated from Example 2 in a way that introduced toluene. Trial Tr. at 1586:18–1587:10 (Myerson Direct 6.24.21); *see also* JTX-43 at JTX-43_29.

1408. Dr. Steed does not opine, one way or the other, whether the experiments Celgene submitted to the EPO faithfully replicated Example 2. Trial Tr. at 1586:9–17 (Myerson Direct 6.24.21).

1409. Dr. Steed does not opine, one way or the other, whether Celgene actually obtained Form C in the experiments submitted to the EPO.

1410. Dr. Sacchetti does not opine, one way or the other, whether the experiments Celgene submitted to the EPO faithfully replicated Example 2.

1411. Dr. Sacchetti does not opine, one way or the other, whether Celgene actually obtained Form C in the experiments submitted to the EPO.

1412. The European Patent Office found that Example 2 would have inherently resulted in apremilast Form B based on the data submitted by Teva, Zentiva, Lek, and Celgene. Trial Tr. at 1143:16–1144:2 (Steed Cross 6.22.21); JTX-225 at JTX-225_17.

c) The '515 Provisional provides a written description sufficient that a POSA would have understood that the inventors were in possession of the solid crystalline apremilast that was the result of Example 2 of the '515 Provisional, which was inherently Form B of apremilast which has an XRPD pattern comprising peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta.

1413. A POSA would have understood at the time the '515 Provisional was filed that the inventors of the '515 Provisional were in possession of the product of Example 2, including

whatever inherent properties it has. Trial Tr. at 1577:2–21 (Myerson Direct 6.24.21); Trial Tr. at 1194:2–5 (Sacchetti Cross 6.22.21); Trial Tr. at 1136:19–1140:13 (Steed Cross 6.22.21).

1414. A POSA would have understood from the disclosure of Example 2 that the inventors were in possession of a crystalline form of apremilast that they could identify via XRPD. Trial Tr. at 1577:2–21 (Myerson Direct 6.24.21); Trial Tr. at 1194:2–5 (Sacchetti Cross 6.22.21).

1415. XRPD analysis of crystalline forms was routine. Trial Tr. at 1577:2–21 (Myerson Direct 6.24.21); Trial Tr. at 1077:15–1079:3, 1124:10–14 (Steed Direct 6.22.21).

1416. Conducting an XRPD analysis results in a "diffraction pattern" that is directly related to the crystal structure of the substance of interest. JSF ¶ 143 (ECF No. 422); *see also* Trial Tr. at 1577:2–21 (Myerson Direct 6.24.21); 1167:18–1168:11 (Sacchetti Direct 6.22.21); 1124:19–1125:7 (Steed Direct 6.22.21); 1138:7–10 (Steed Cross 6.22.21).

1417. A POSA reading the '515 Provisional would have understood that the XRPD pattern generated by XRPD analysis on the product of Example 2 provides a unique signature that is inherent to the crystalline form being investigated, and can be used to distinguish the given polymorphic form from other polymorphic forms of the substance. JSF ¶ 143 (ECF No. 422); *see also* Trial Tr. at 1577:2–21 (Myerson Direct 6.24.21); 1167:18–1168:11 (Sacchetti Direct 6.22.21); 1124:19–1125:7 (Steed Direct 6.22.21); 1138:11–1139:2 (Steed Cross 6.22.21).

1418. A POSA would recognize the inventors were in possession of a crystalline form of apremilast of Example 2 with inherent XRPD peaks, as of March 20, 2002, from the '515 Provisional. Trial Tr. at 1587:13–24 (Myerson Direct 6.24.21).

1419. A POSA would understand that XRPD peaks, including the peaks recited in claim 1 of the '101 Patent are inherent property of Form B. Trial Tr. at 1587:13–24 (Myerson Direct 6.24.21).

1420. Dr. Steed did not form an opinion one way or the other on whether inherent properties need to be disclosed in an application that show that inventors were in possession of the invention. Trial Tr. at 1140:17–1142:10 (Steed Cross 6.22.21).

1421. Because Example 2 is word for word the same in the '515 Provisional and all of the applications and patents in the chain from the '515 Provisional to the '101 Patent, the '515 Provisional provides written description support for claims 1 and 15 of the '101 Patent. PF ¶¶ 1369–70, 1372–1420.

d) The '515 Provisional enables a POSA to make the solid crystalline apremilast that was the result of Example 2 of the '515 Provisional, which was inherently Form B of apremilast which has an XRPD pattern comprising peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2 theta, without undue experimentation.

1422. Example 2 of the '515 Provisional enables a POSA to create Form B without undo experimentation. Trial Tr. at 1587:13–24 (Myerson Direct 6.24.21). This is demonstrated by the EPO data submitted by Teva, Zentiva, and Lek. PF ¶¶ 1383–1412. In addition, while Dr. Sacchetti disagreed with Dr. Myerson regarding the identity of the crystalline form produced by Example 2, he testified that Example 2 of the '515 Provisional enables a POSA to make the product of Example 2 without undue experimentation. Trial Tr. at 1194:2–9 (Sacchetti Cross 6.22.21).

1423. Dr. Steed did not offer an opinion that Example 2 does not enable claims 1 and 15 of the '101 Patent. Trial Tr. at 1590:22–24 (Myerson Direct 6.24.21); Trial Tr. at 1136:11–13 (Steed Cross 6.22.21).

1424. Because Example 2 is word for word the same in the '515 Provisional and all of the applications and patents in the chain from the '515 Provisional to the '101 Patent, the '515 Provisional provides written description support for claims 1 and 15 of the '101 Patent. PF ¶¶ 1369–70, 1372–1412, 1422–23.

2. The ’052 Publication is not prior art to claims 1 and 15 of the ’101 Form B Patent.

1425. The ’052 Publication was published on October 2, 2003. DTX-179 at DTX-179_1; *see also* Trial Tr. at 1591:18–1592:23 (Myerson Direct 6.24.21).

1426. Because claims 1 and 15 of the ’101 Patent are entitled to a priority date of March 20, 2002, the ’052 Publication is not prior art to claims 1 and 15. Trial Tr. at 1591:18–1592:23 (Myerson Direct 6.24.21); 1130:17–1131:10 (Steed Cross 6.22.21).

a) Claims 1 and 15 of the ’101 Form B Patent are not obvious based on the references relied on by Defendants.

1427. The only combinations of references on which Dr. Steed offered obviousness opinions are (1) the ’052 Publication and the “Knowledge of a POSA,” and (2) the ’052 Publication in combination with Brittain 1997, ICH Guidelines, Guillory, Brittain 1999, and the “Knowledge of a POSA,” both of which rely on the ’052 Publication. Trial Tr. at 1125:15–1126:4 (Steed Direct 6.22.21).

1428. Because the ’052 Publication is not prior art to claims 1 and 15 of the ’101 Patent, claims 1 and 15 are not obvious over ’052 Publication and the “Knowledge of a POSA,” or the ’052 Publication in combination with Brittain 1997, ICH Guidelines, Guillory, Brittain 1999, and the “Knowledge of a POSA.” Trial Tr. at 1591:18–1592:23 (Myerson Direct 6.24.21); 1130:17–1131:10 (Steed Cross 6.22.21).

1429. Dr. Steed did not argue that claims 1 and 15 of the ’101 Patent are obvious if claims 1 and 15 are entitled to a priority date of March 20, 2002.

1430. Dr. Steed did not offer any opinions on the ’358 Patent.

1431. Dr. Steed did not offer any invalidity opinions on the ’049 Publication.

1432. Dr. Steed did not offer any invalidity combinations that include Bryn 1995 or Bryn 1999.

3. Defendants have failed to prove that the '101 Form B Patent is invalid for obviousness-type double patenting.

1433. Before trial, Defendants limited their ODP challenge to claims 1 and 15 of the '101 Patent to two references: Claim 1 of the '243 Patent and Claim 1 of the '606 Patent. Joint Final Pretrial Order at 111 ¶¶ 79–80 (ECF No. 422).

1434. At trial, Defendants further narrowed their challenge to a single reference: Claim 1 of the '243 Patent. Trial Tr. at 1128:17–1129:21 (Steed Direct 6.22.21).

1435. Defendants did not introduce the '606 Patent (marked as JTX-220) into evidence and offered no evidence that the inventions claimed by Claims 1 and 15 of the '101 Patent are patentably indistinct from the invention claimed by Claim 1 of the '606 Patent.

1436. Furthermore, were it relevant, the Court would find that Defendants have failed to carry their burden to adduce clear and convincing evidence to show that the invention claimed by Claims 1 and 15 of the '101 Patent is patentably indistinct from the improvement claimed by Claim 1 of the '606 Patent because Defendants offered no evidence.

a) The difference in expiration dates between the '101 Form B Patent and the '243 Patent is solely attributable to a statutorily authorized time extension.

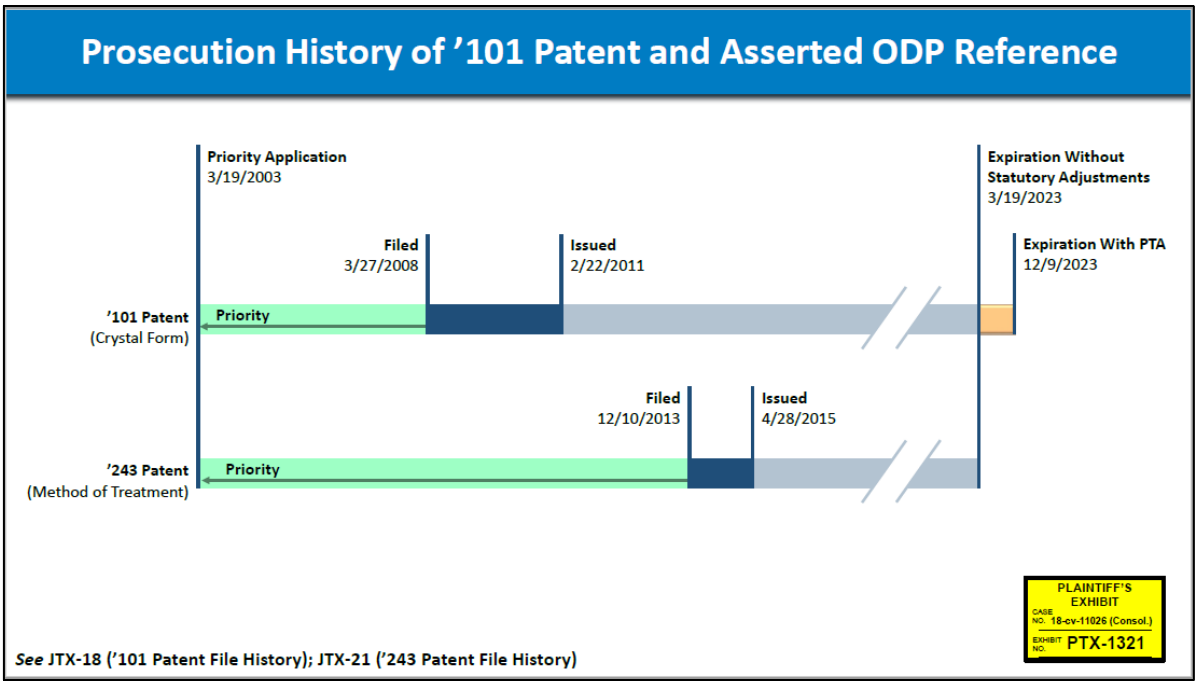
1437. The application for the '101 Patent was filed on March 27, 2008. Trial Tr. at 1543:9–1544:7, 1550:8–16 (Smith Direct 6.24.21); PTX-1321. The '101 Patent issued on February 22, 2011, and it will expire on December 9, 2023. *Id.* The '101 Patent claims priority to the application for the '940 Patent, which was filed on March 19, 2003. *Id.*

1438. The application for the '243 Patent was filed on December 10, 2023. Trial Tr. at 1550:17–25 (Smith Direct 6.24.21); PTX-1321. The '243 Patent issued on April 28, 2015, and it will expire on March 19, 2023. *Id.* The '243 Patent claims priority to the application for the '940 Patent, which was filed on March 19, 2003. *Id.*

1439. The '101 Patent expires later than the '243 Patent solely because the '101 Patent received a statutorily authorized time extension: a PTA of 265 days. Trial Tr. at 1541:10–15,

1543:9–1544:7, 1545:23–1546:6, 1550:8–16, 1551:1–10 (Smith Direct 6.24.21); PTX-1316; PTX-1321.

1440. The key events in the file histories of the ’101 and ’243 Patents are reflected in the timeline below, PTX-1321:



1441. It is undisputed that the statutorily authorized time extension that the ’101 Patent received was properly calculated and awarded pursuant to the applicable Patent Office policies, practices, and procedures. Trial Tr. at 1545:23–1546:6 (Smith Direct 6.24.21); PTX-1316.

1442. The ’101 Patent was entitled to, and received, 265 days of PTA. Trial Tr. at 1545:23–1546:6 (Smith Direct 6.24.21); PTX-1316.

1443. The Patent Office missed one applicable deadline during its examination of the application for the ’101 Patent: it issued a first office action 265 days after the 14-month deadline. Trial Tr. at 1544:8–1545:9 (Smith Direct 6.24.21); PTX-1316. There were no days of applicant delay. Trial Tr. at 1545:10–17 (Smith Direct 6.24.21); PTX-1316.

1444. The total PTA to which a patent is entitled is equal to the sum of Patent Office delay, minus any applicant delay, which is 265 days in total for the ’101 Patent. Trial Tr. at 1545:23–1546:6 (Smith Direct 6.24.21); PTX-1316.

1445. Celgene did not file a terminal disclaimer in connection with the ’101 Patent, tying its expiration to the expiration of the ’243 Patent. Trial Tr. at 1546:13–17 (Smith Direct 6.24.21).

1446. But for the statutorily authorized time extension it received—a PTA of 265 days—the ’101 Patent would expire on the same day as the ’243 Patent: March 19, 2023. Trial Tr. at 1541:10–15, 1543:9–1544:7, 1545:23–1546:6, 1550:8–16, 1551:1–10 (Smith Direct 6.24.21); PTX-1316; PTX-1321.

1447. The ’243 Patent is not a proper double-patenting reference for the ’101 Patent because the difference in expiration dates between the ’101 Patent and the ’243 Patent is solely attributable to a statutorily authorized time extension.

b) The difference in expiration dates between the ’101 Form B Patent and the ’243 Patent is not the result of any prosecution gamesmanship.

1448. It would be inequitable to apply double patenting in the particular circumstances of this case because the difference in expiration dates between the ’101 and ’243 Patents is not the result of any prosecution gamesmanship. Trial Tr. at 1541:10–15, 1551:11–1552:1 (Smith Direct 6.24.21).

1449. Defendants do not contend that the difference in expiration dates between the ’101 and ’243 Patents is the result of prosecution gamesmanship and have not offered any evidence of such gamesmanship. Trial Tr. at 1552:2–8 (Smith Direct 6.24.21).

1450. The difference in expiration dates between the ’101 and ’243 Patents is not the result of strategic delay. Trial Tr. at 1551:11–15 (Smith Direct 6.24.21).

1451. The ’101 Patent is a post-GATT patent, so its expiration date is not tied to its issue date. Trial Tr. at 1543:9–1544:7 (Smith Direct 6.24.21).

1452. Celgene did not intentionally delay issuance of the ’101 Patent. Trial Tr. at 1545:10–17, 1551:11–15 (Smith Direct 6.24.21); PTX-1316.

1453. The difference in expiration dates between the '101 and '243 Patents is also not the result of structuring priority claims. Trial Tr. at 1551:16–22 (Smith Direct 6.24.21).

1454. The '101 and '243 Patents each claim priority to a common prior application, so—but for any statutory extensions—they would expire on the same date. Trial Tr. at 1551:16–22 (Smith Direct 6.24.21); PTX-1316.

1455. Celgene made a priority claim for the '101 Patent by filing the application as a continuation-in-part, which started the 20-year term of the patent on an earlier date. Trial Tr. at 1542:5–1543:2, 1544:1–7 (Smith Direct 6.24.21).

1456. More broadly, the undisputed evidence establishes that the difference in expiration dates between the '101 and '243 Patents is not the result of any form of prosecution gamesmanship or any improper conduct by Celgene. Trial Tr. at 1541:10–15, 1551:23–1552:1 (Smith Direct 6.24.21).

1457. Additional considerations show that it would be particularly inequitable to apply double patenting in the circumstances of this case.

1458. Defendants offered no evidence that the improvement claimed by Claim 1 of the '243 Patent (methods of treating disease with a crystal form of stereomerically pure apremilast) is patentably indistinct from the basic inventions claimed by Claims 1 and 15 of the '101 Patent (crystal forms of stereomerically pure apremilast). Dr. Steed's testimony did not address this question. Trial Tr. at 1129:1–21 (Steed Direct 6.22.21).

1459. Celgene pursued the improvement claimed in the '243 Patent years after the '101 Patent issued. Trial Tr. at 1550:8–25 (Smith Direct 6.24.21); PTX-1321.

1460. It would be inequitable for the '243 Patent to cut short the term of patent protection over the basic inventions claimed by the '101 Patent, solely because of delays to the prosecution of the '101 Patent that were outside Celgene's control and not the product of any gamesmanship by Celgene.

c) Defendants have failed to carry their burden on patentable distinctness.

1461. Defendants have failed to carry their burden to adduce clear and convincing evidence to show that the basic inventions claimed by Claims 1 and 15 of the ’101 Patent (crystal forms of stereomerically pure apremilast) are patentably indistinct from the improvement claimed by Claim 1 of the ’243 Patent (methods of treating disease with a crystal form of stereomerically pure apremilast).

1462. Defendants’ only evidence is the testimony of Dr. Steed. However, rather than considering the subject matter of the claims as a whole, Dr. Steed focused on comparing aspects of the language or wording of the claims in each patent. Trial Tr. at 1129:1–21 (Steed Direct 6.22.21).

1463. Dr. Steed’s testimony regarding the ’101 and ’243 Patents did not mention patentable distinctness. Trial Tr. at 1129:1–1129:21 (Steed Direct 6.22.21).

1464. Neither Dr. Steed nor any other witness testified that the inventions claimed in Claims 1 and 15 of the ’101 Patent are patentably indistinct from, or obvious over, Claim 1 of the ’243 Patent.

XIII. THE ASSERTED CLAIMS OF THE ’283 FORM A PATENT ARE INFRINGED AND NOT INVALID

A. Person of Ordinary Skill in the Art

1465. The person of ordinary skill in the art for purposes of the ’283 Patent is the same as the POSA for the ’101 Patent. Trial Tr. at 437:13–21 (Myerson Direct 6.16.21); 1587:25–1588:4 (Myerson Direct 6.24.21).

1466. The person of ordinary skill in the art for purposes of the ’283 Patent is an individual with a bachelor’s degree in chemistry, chemical engineering, or a related discipline, with some knowledge of crystalline solid forms and their characterization, and several years of experience in the pharmaceutical industry; or an advanced degree in the above listed

disciplines, with some knowledge of solid-state chemistry or analytical chemistry and less experience. Trial Tr. at 437:13–21 (Myerson Direct 6.16.21); 1587:25–1588:4 (Myerson Direct 6.24.21).

1467. The definition of a POSA offered by Amgen's expert, Prof. Myerson, differs slightly from the definition proposed by Defendants' expert, Prof. Steed, and Zydus's expert, Dr. Sacchetti. Trial Tr. at 1070:23–1071:1 (Steed Direct 6.22.21); 587:13–588:1 (Gribble Direct 6.18.21) (providing the definition of a POSA adopted by Dr. Steed in his analysis); 1174:13–21 (Sacchetti Direct 6.22.21); Trial Tr. at 1588:5–10 (Myerson Direct 6.24.21).

1468. Prof. Myerson's opinions would not have been different had he applied Prof. Steed's or Dr. Sacchetti's definitions. Trial Tr. at 1588:8–10 (Myerson Direct 6.24.21).

B. Technology Background

1469. The technology background for the '283 Patent is the same as for the '101 Patent. *See* PF ¶¶ 1208–30.

C. Zydus Infringes Claims 2 and 27 of the '283 Form A Patent.

1470. The submission of Zydus's ANDA to the FDA seeking approval for Zydus's ANDA Products is an act of infringement with respect to claims 2 and 27 of the '283 Patent under 35 U.S.C. § 271(e)(2)(A), if those claims are not found to be invalid or unenforceable. Civ. No. 18-11267, ECF No. 54; ZSF (A2) ¶ 14 (ECF No. 422).

1471. Upon final approval of Zydus's ANDA, the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Zydus's ANDA Products will infringe claims 2 and 27 of the '283 Patent under 35 U.S.C. § 271(a), (b) and/or (c), if those claims are not found to be invalid or unenforceable. Civ. No. 18-11267, ECF No. 54; ZSF (A2) ¶ 15 (ECF No. 422).

D. Zydus Has Failed to Prove by Clear and Convincing Evidence that Claims 2 and 27 of the ’283 Form A Patent Are Invalid.

1. Zydus has failed to prove by clear and convincing evidence that claims 2 and 27 of the ’283 Form A Patent are anticipated.

a) Claims 2 and 27 of the ’283 Form A Patent are not anticipated by the ’052 Publication because Example 2 inherently results in Form B, not Form A.

1472. Dr. Sacchetti did not argue that the ’052 Publication expressly discloses Form A or Form A with the XRPD peaks recited in the claims. Trial Tr. at 1192:24–1193:1 (Sacchetti Cross 6.22.21).

1473. The ’052 Publication does not inherently disclose Form A because it results in Form B. PF ¶¶ 1474–1507.

1474. Example 2 inherently discloses Form B of apremilast. Trial Tr. at 1571:23–1572:9 (Myerson Direct 6.24.21).

1475. When practiced by a POSA, Example 2 of the ’515 Provisional inherently results in Form B of apremilast. PF ¶¶ 1476–1507.

1476. Every experiment in the record that faithfully replicated Example 2 resulted in Form B. PF ¶¶ 1477–1507.

1477. As demonstrated by experiments faithfully replicating Example 2 that were submitted to the EPO, if a POSA replicates Example 2, which uses a 2:1 ratio of ethanol to acetone, Form B is always obtained, regardless of whether fast cooling or slow cooling is utilized. Trial Tr. at 1596:17–22 (Myerson Direct 6.24.21).

1478. Teva, Zentiva, and Lek submitted a total of 13 experiments to the European Patent Office (“EPO”) as part of an opposition proceeding to European Patent No EP-B-2276483. Trial Tr. at 1577:25–1578:17 (Myerson Direct 6.24.21); JTX-225 at JTX-225_1–2.

1479. Teva’s experiments were a faithful replication of Example 2 based on a comparison of Teva’s experimental procedure to Example 2. Each of Teva’s experiment used

a solvent system that was a 2:1 ratio of ethanol to acetone. Trial Tr. at 1578:18–1579:19 (Myerson Direct 6.24.21); JTX-43 at JTX-43_29; JTX-225 at JTX-225_39; *see also* Trial Tr. at 1144:4–19 (Steed Cross 6.22.21).

1480. Teva created four replications of Example 2, each of which resulted in Form B of apremilast as determined by XRPD analysis. Trial Tr. at 1579:20–22, 1580:9–22 (Myerson Direct 6.24.21); 1143:13–15, 1145:7–12 (Steed Cross 6.22.21); 1201:6–9 (Sacchetti Cross 6.22.21); JTX-225 at JTX-225_36, _46.

1481. Teva's experimental conditions replicating Example 2 covered different variations a POSA may have used in carrying out Example 2. JTX-225 at JTX-225_15 ("[T]he experimental data supplied by [Teva, Zentiva, and Lek] seem to be straight forward possibilities for the skilled person having the information disclosed in [Example 2] within the reasonable variations possible."); JTX-225 at JTX-225_17 ("[T]he experiments done by [Teva, Zentiva, and Lek] deem to be straight forward option for a chemist having the information of [Example 2] in hands" and varied "different parameters like solvent purity, temperature, rate of cooling and duration of crystal formation."); Trial Tr. at 1580:13–22 (Myerson Direct 6.24.21).

1482. Teva's replications demonstrate that when Example 2 is performed, using the 2:1 ratio of ethanol to acetone set forth in Example 2, with both fast cooling and slow cooling, it generates From B of apremilast. Two of Teva's four replications of Example 2 were performed using fast cooling, both of which resulted in Form B. Trial Tr. at 1580:9–22 (Myerson Direct 6.24.21); JTX-225 at JTX-225_13–14, _39–41, _46; *see also* Trial Tr. at 1201:14–18 (Sacchetti Cross 6.22.21).

1483. Zentiva's experiment was a faithful replication of Example 2 based on a comparison of Zentiva's experimental procedure to Example 2. Zentiva's experiment used a solvent system that was a 2:1 ratio of ethanol to acetone. Trial Tr. at 1580:23–1581:15

(Myerson Direct 6.24.21); JTX-43 at JTX-43_29; JTX-225 at JTX-225_52; *see also* Trial Tr. at 1144:4–19 (Steed Cross 6.22.21).

1484. Zentiva's replication of Example 2 resulted in Form B of apremilast as determined by XRPD analysis. Trial Tr. at 1581:16–1582:3 (Myerson Direct 6.24.21); 1143:13–15, 1145:7–12 (Steed Cross 6.22.21); 1201:6–9 (Sacchetti Cross 6.22.21); JTX-225 at JTX-225_352–53.

1485. Zentiva's experimental conditions replicating Example 2 covered conditions a POSA may have used in carrying out Example 2. JTX-225 at JTX-225_15 ("[T]he experimental data supplied by [Teva, Zentiva, and Lek] seem to be straight forward possibilities for the skilled person having the information disclosed in [Example 2] within the reasonable variations possible."); JTX-225 at JTX-225_17 ("[T]he experiments done by [Teva, Zentiva, and Lek] deem to be straight forward option for a chemist having the information of [Example 2] in hands" and varied "different parameters like solvent purity, temperature, rate of cooling and duration of crystal formation."); Trial Tr. at 1581:21–1582:3 (Myerson Direct 6.24.21).

1486. Zentiva's replications demonstrate that when Example 2 is performed, using the 2:1 ratio of ethanol to acetone set forth in Example 2, with fast cooling, it generates From B of apremilast. Zentiva's replication of Example 2 was performed using fast cooling (according to Dr. Sacchetti's definition of fast cooling), which resulted in Form B. Trial Tr. at 1581:16–1582:3 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14, _53; *see also* Trial Tr. at 1201:14–18 (Sacchetti Cross 6.22.21).

1487. Lek's experiments were a faithful replication of Example 2 as demonstrated by comparing Lek's experimental procedure to Example 2. Each of Lek's experiment used a solvent system that was a 2:1 ratio of ethanol to acetone. Trial Tr. at 1582:4–1583:24 (Myerson

Direct 6.24.21); JTX-43 at JTX-43_29; JTX-225 at JTX-225_65; *see also* Trial Tr. at 1144:4–19 (Steed Cross 6.22.21).

1488. Lek is a subsidiary of Sandoz. JTX-225 at JTX-225_64.

1489. Lek created eight replications of Example 2, all of which resulted in Form B of apremilast as determined by XRPD analysis. Trial Tr. at 1583:14–24 (Myerson Direct 6.24.21); 1143:13–15, 1145:7–12 (Steed Cross 6.22.21); 1201:6–9 (Sacchetti Cross 6.22.21); JTX-225 at JTX-225_64, _66.

1490. Lek's experimental conditions replicating Example 2 covered different variations a POSA may have used in carrying out Example 2. JTX-225 at JTX-225_15 ("[T]he experimental data supplied by [Teva, Zentiva, and Lek] seem to be straight forward possibilities for the skilled person having the information disclosed in [Example 2] within the reasonable variations possible."); JTX-225 at JTX-225_17 ("[T]he experiments done by [Teva, Zentiva, and Lek] deem to be straight forward option for a chemist having the information of [Example 2] in hands" and varied "different parameters like solvent purity, temperature, rate of cooling and duration of crystal formation."); Trial Tr. at 1583:14–24 (Myerson Direct 6.24.21).

1491. Lek's replications demonstrate that when Example 2 is performed, using the 2:1 ratio of ethanol to acetone set forth in Example 2, with both fast cooling and slow cooling, it generates From B of apremilast. Four of Lek's eight replications of Example 2 were performed using fast cooling, both of which resulted in Form B. Trial Tr. at 1583:14–24 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14, _66; *see also* Trial Tr. at 1201:14–18, 1201:25–1202:5 (Sacchetti Cross 6.22.21).

1492. The EPO data submitted by Teva, Zentiva, and Lek demonstrates that crystalline form of apremilast obtained when a POSA practices Example 2 always results in Form B. Trial Tr. at 1587:13–24 (Myerson Direct 6.24.21). Teva's, Zentiva's, and Lek's experiments

included replications that used fast cooling, which all resulted in Form B, demonstrating that when Example 2 is practiced with fast cooling, it yields Form B. Trial Tr. at 1596:17–1597:10 (Myerson Direct 6.24.21).

1493. While Celgene also submitted the results of an attempt to replicate Example 2 to the EPO as part of opposition proceeding to European Patent No EP-B-2276483, that experiment did not properly replicate Example 2. Trial Tr. at 1584:4–7 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14–15.

1494. Celgene's experiments deviated from the requirements of Example 2 by using a starting material having 100% ee instead of 98% ee as required by Example 2 and thus were not faithful replications of Example 2. Trial Tr. at 1584:10–16 (Myerson Direct 6.24.21); JTX-225 at JTX-225_14–15.

1495. The European Patent Office stated that Celgene's use of a 100% ee starting material "will influence the outcome of crystallization" and "purity of an API used in recrystallization may have an impact on the outcome of recrystallization." Trial Tr. at 1584:4–16 (Myerson Direct 6.24.21); JTX-225 at JTX-225_15; *see also* Trial Tr. at 1145:21–1147:11 (Steed Cross 6.22.21).

1496. The purity of a starting material can have a meaningful influence on crystallization and the polymorphic outcome of the crystallization. Trial Tr. at 1584:18–1586:5 (Myerson Direct 6.24.21); DTX-125 at DTX-125_22 ("The presence of impurities can have a profound effect on the growth of crystals . . . . Some impurities can exert an influence at very low concentrations (less than one part per million)."); *see also* Trial Tr. at 1611:7–19 (Myerson Direct 6.24.21) (explaining that a new polymorph of ritonavir was unexpectedly discovered due to small change in the impurity profile of the starting material in the crystallization manufacturing process).

1497. The difference between 98% ee and 100% ee is 1% enantiomeric purity, which is a 10,000 parts per million difference. Trial Tr. at 1584:10–16, 1584:21–1585:2, 1586:3–5 (Myerson Direct 6.24.21).

1498. Celgene's experiments used continuous scratching over five hours, which is not a procedure that a POSA would have used. Continuous scratching means that the scientist was taking a rod and putting it inside the crystallization vessel and rubbing the side of the inside to help induce crystallization for five hours, which is not a typical thing a POSA would do. Trial Tr. at 1584:21–1585:10 (Myerson Direct 6.24.21).

1499. The results Celgene reported for its experiment indicate that it made a mistake in conducting the experiment or analyzing the results. Celgene represented to the EPO that it obtained Form C from its experiments. Trial Tr. at 1586:9–1587:10 (Myerson Direct 6.24.21); JTX-225 at JTX-225_15.

1500. Form C is a crystalline form of apremilast described in the '101 Patent that is a toluene solvate, which means that it contains toluene as part of the crystalline structure. A solvate like Form C cannot be made unless the solvent, here toluene, is present as part of the experiment. Trial Tr. at 1586:9–1587:10 (Myerson Direct 6.24.21); JTX-5 at 21:66–22:3.

1501. Toluene is not part of Example 2 and therefore cannot be part of any crystalline apremilast that is created from a faithful replication of Example 2. *E.g.*, JTX-43 at JTX-43_29; Trial Tr. at 1586:18–1587:10 (Myerson Direct 6.24.21).

1502. Celgene is either mistaken that it obtained Form C, or mistakenly deviated from Example 2 in a way that introduced toluene. Trial Tr. at 1586:18–1587:10 (Myerson Direct 6.24.21); *see also* JTX-43 at JTX-43_29.

1503. Dr. Steed does not opine, one way or the other, whether the experiments Celgene submitted to the EPO faithfully replicated Example 2. Trial Tr. at 1586:9–17 (Myerson Direct 6.24.21).

1504. Dr. Steed does not opine, one way or the other, whether Celgene actually obtained Form C in the experiments submitted to the EPO.

1505. Dr. Sacchetti does not opine, one way or the other, whether the experiments Celgene submitted to the EPO faithfully replicated Example 2.

1506. Dr. Sacchetti does not opine, one way or the other, whether Celgene actually obtained Form C in the experiments submitted to the EPO.

1507. The European Patent Office found that Example 2 would have inherently resulted in apremilast Form B based on the data submitted by Teva, Zentiva, Lek, and Celgene. Trial Tr. at 1143:16–1144:2 (Steed Cross 6.22.21); JTX-225 at JTX-225_17.

1508. The '283 Patent does not state or suggest that Form A will always be obtained from all ratios of ethanol and acetone or that Form A will always be obtained from all ratios of ethanol and acetone when using fast cooling. Trial Tr. at 1594:19–1595:17 (Myerson Direct 6.24.21).

1509. The '283 Patent states that "In certain embodiments, Form A of [apremilast] can be obtained from various solvents, including, but not limited to, solvent systems comprising acetone, ethanol, and mixtures thereof. In certain embodiments, Form A can be obtained using a fast cooling process." JTX-6 at 18:32–38; Trial Tr. at 1594:21–1595:1 (Myerson Direct 6.24.21). A POSA would have understood from that passage that some solvent systems comprising acetone, ethanol, or both acetone and ethanol, along with fast cooling, could generate Form A, but not that all such solvent systems would always generate Form A. Trial Tr. at 1594:19–1595:17 (Myerson Direct 6.24.21).

1510. The passage "In certain embodiments, Form A of [apremilast] can be obtained from various solvents, including, but not limited to, solvent systems comprising acetone, ethanol, and mixtures thereof. In certain embodiments, Form A can be obtained using a fast cooling process," JTX-6 at 18:32–38, does not state that pure ethanol and pure acetone can be

used to make Form A. It states that solvent systems "comprising" ethanol or acetone can be used to make Form A. "Comprising" means that other components can be included. Thus, the statement effectively means that solvent systems that include ethanol and other solvents or acetone and other solvents can make Form A. Trial Tr. at 1594:19–1595:17 (Myerson Direct 6.24.21).

1511. The '283 Patent states that "In certain embodiments, Form B of [apremilast] can be obtained from various solvents, including, but not limited to, solvent systems comprising … acetone … ethanol … and mixtures comprising two or more thereof," meaning that Form B can also be made from solvents systems comprising acetone and ethanol. Trial Tr. at 1595:22–1596:7 (Myerson Direct 6.24.21); JTX-6 at 19:54–67. That passage confirms that some solvent systems with both acetone and ethanol generate Form B, instead of Form A.

1512. The fact that the passage "In certain embodiments, Form B of [apremilast] can be obtained from various solvents, including, but not limited to, solvent systems comprising … acetone . . . ethanol . . . and mixtures comprising two or more thereof," JTX-6 at 19:54–67, relating to Form B, does not reference fast cooling does not mean that solvent systems containing ethanol and acetone do not make Form B when fast cooling is used. The passage does not specify a cooling rate, which would indicate to a POSA that different cooling rates could be used to make Form B, including fast cooling. Trial Tr. at 1595:18–1596:22 (Myerson Direct 6.24.21). This understanding is confirmed by the experiments by Teva, Zentiva, and Lek, which showed that a mixture of ethanol and acetone with a 2:1 ratio of ethanol to acetone using fast cooling makes Form B. PF ¶¶ 1479, 1482–83, 1486–87, 1491–92; Trial Tr. at 1596:17–1597:10 (Myerson Direct 6.24.21).

1513. Consistent with the teachings of the '283 Patent, Form A can be obtained from a fast cooling recrystallization from a solvent system containing a 10:1 ratio of ethanol to

acetone, as demonstrated by a synthesis of Form A conducted by Triclinic Labs. DTX-Zydus-56 at DTX-Zydus-56_4; *see also* Trial Tr. 464:14–465:18 (Myerson Cross 6.16.21).

b) There is no evidence that the results of the experiments Teva, Zentiva, and Lek submitted, which obtained Form B, were caused by seeding.

1514. There is no evidence that any of Teva's, Zentiva's, or Lek's experiments replicating Example 2 that were submitted to the EPO were seeded (inadvertently or otherwise) with Form B. Trial Tr. at 1606:13–19 (Myerson Direct 6.24.21).

1515. Inadvertent seeding is a result generally of poor laboratory practice where a laboratory has performed an experiment with one crystalline form of a compound, and has not properly cleaned the laboratory equipment or the hood or laboratory workspace in which the prior experiment was conducted, which results in left-over material that can inadvertently contaminate a later experiment. Trial Tr. at 1604:24–1605:4 (Myerson Direct 6.24.21).

1516. There is no evidence that any of Teva, Zentiva, or Lek used Form B prior to conducting the experiments replicating Example 2 that were submitted to the EPO. Trial Tr. at 1205:2–7 (Sacchetti Cross 6.22.21).

1517. There is no evidence that any of Teva, Zentiva, or Lek had Form B present in their laboratories prior to conducting the experiments replicating Example 2 that were submitted to the EPO. Trial Tr. at 1202:15–1205:7 (Sacchetti Cross 6.22.21).

1518. There is no evidence that any of Teva, Zentiva, or Lek used poor laboratory practice before or during the experiments replicating Example 2 that were submitted to the EPO. Trial Tr. at 1606:13–19 (Myerson Direct 6.24.21).

1519. Dr. Sacchetti's seeding theory would mean that three different companies (Teva, Zentiva, and Lek), in three different locations, all practiced poor laboratory practices and all had Form B in their laboratories despite no evidence that any of those companies used

Form B at the time of the experiments. Trial Tr. at 1606:13–19 (Myerson Direct 6.24.21). That is implausible.

1520. The results of the experiments by Teva, Zentiva, and Lek were not affected by seeding. PF ¶¶ 1514–19.

1521. Scientists at Triclinic Labs successfully made Form A of apremilast using Form B as a starting material without using hot filtration or refluxing the solvents, demonstrating that the presence of Form B did not inadvertently seed the Triclinic Labs experiment. DTX-Zydus-56 at DTX- Zydus-56_4 (Sample TCL11958 is Apremilast Form B; Table 2 states Sample TCL11958 (i.e., Form B) was the starting material to make 897-13-1, which was then used to make Form A (sample 897-14-1)); *see also* Trial Tr. at 464:14–465:18 (Myerson Cross 6.16.21) (explaining that Triclinic Labs obtained Form A using the experimental procedure described in DTX-Zydus-56 at DTX-Zydus-56_4).

1522. Example 2 does not mention reflux or hot filtration as part of the recrystallization step described in the example. Reflux and hot filtration are not part of the recrystallization step described in Example 2. Trial Tr. at 1606:1–12 (Myerson Direct 6.24.21); JTX-43 at JTX-43_29.

1523. Dr. Sacchetti's testimony that reflux and hot filtration are required is based on the purported ability of those practices to eliminate seeding. Trial Tr. at 1188:4–17 (Sacchetti Direct 6.22.21). While Dr. Sacchetti opined that refluxing or hot filtering would have eliminated any inadvertent seeding, there was no evidence to suggest seeding had occurred.

1524. Reflux means heating a solvent system to boiling. Trial Tr. at 1605:18–23 (Myerson Direct 6.24.21).

1525. There is no evidence that Example 2 ever results in Form A of apremilast.

1526. Dr. Sacchetti formed his opinion that Example 2 inherently results in Form A prior to becoming aware of Teva's, Zentiva's, and Lek's experiments replicating Example 2

that were submitted to the EPO. Trial Tr. at 1198:16–1199:16, 1202:10–14 (Sacchetti Cross 6.22.21).

2. Zydus has failed to prove by clear and convincing evidence that claims 2 and 27 of the '283 Form A Patent are invalid for obviousness.

a) Claims 2 and 27 of the '283 Form A Patent are not obvious over the '052 Publication in combination with Byrn 1994, Guillory, Fieser, and the "knowledge of a POSA."

(1) Conducting Example 2 using a 2:1 ratio of ethanol to acetone using fast cooling results in Form B, not Form A.

1527. Dr. Sacchetti does not contend that a POSA would have modified the 2:1 ratio of ethanol to acetone prescribed in Example 2. *See* Trial Tr. at 1188:23–1191:2 (Sacchetti Direct 6.22.21).

1528. As demonstrated by experiments faithfully replicating Example 2 that were submitted to the EPO, if a POSA replicates Example 2, which uses a 2:1 ratio of ethanol to acetone, Form B is always obtained, regardless of whether fast cooling or slow cooling is utilized. Trial Tr. at 1596:17–22 (Myerson Direct 6.24.21); *see also* PF ¶¶ 1477–92.

(2) A POSA would not have had a reasonable expectation of success at achieving Form A because Form A was not known and polymorphism is highly unpredictable.

1529. Polymorphism is highly unpredictable. Trial Tr. at 1609:14–1611:19 (Myerson Direct 6.24.21); Trial Tr. at 1149:2–1152:5 (Steed Cross 6.22.21); PTX-1114 at PTX-1114_260 ("Every compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be.").

1530. In 2002, 2008, and even today, a POSA would understand that crystalline properties of a crystalline cannot be predicted prior to the discovery of the crystalline form.

Trial Tr. at 1609:14–1610:13 (Myerson Direct 6.24.21); 1150:4–1151:3, 1152:6–1153:3 (Steed Cross 6.22.21); PTX-1114 at PTX-1114_260 ("[E]very compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be.").

1531. In 2002, 2008, and even today, a POSA would understand that the existence or properties of any specific crystalline form cannot be predicted in advance. Trial Tr. at 1609:14–1610:13 (Myerson Direct 6.24.21); 1153:14–22 (Steed Cross 6.22.21); PTX-1114 at PTX-1114_260 ("[E]very compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be.").

1532. In 2002, 2008, and even today, a POSA would understand that the crystallization conditions that will result in a specific crystalline form cannot be predicted in advance. Trial Tr. at 1609:14–1610:13 (Myerson Direct 6.24.21); 1153:23–1154:4 (Steed Cross 6.22.21); PTX-1114 at PTX-1114_260 ("[E]very compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be.").

1533. In 2002, 2008, and even today, a POSA would understand that whether all potential polymorphs of a compound have been created cannot be known. Trial Tr. at 1609:14–1611:19 (Myerson Direct 6.24.21); 1154:7–17 (Steed Cross 6.22.21); DTX-103 at DTX-103_65 ("[E]ven a systematic search may not always reveal all of the polymorphs of a

substance because so many factors, as we have seen, can affect polymorph nucleation and growth.”).

1534. In 2002, 2008, and even today, a POSA would understand that whether a compound is polymorphic cannot be known until two or more polymorphs have actually been created. Trial Tr. at 1609:14–1610:13 (Myerson Direct 6.24.21); 1154:18–22 (Steed Cross 6.22.21); PTX-1114 at PTX-1114_260 (“[E]very compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be.”).

1535. In 2002, 2008, and even today, a POSA would understand that whether more than one polymorph of a given compound can be created cannot be known in advance of conducting experiments. Trial Tr. at 1609:14–23 (Myerson Direct 6.24.21); 1155:2–5 (Steed Cross 6.22.21); PTX-1114 at PTX-1114_260 (“[E]very compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be.”); DTX-103 at DTX-103_65 (“[E]ven a systematic search may not always reveal all of the polymorphs of a substance because so many factors, as we have seen, can affect polymorph nucleation and growth.”).

1536. A polymorph screen is a campaign of experimental tests that can include hundreds or thousands of experiments. Trial Tr. at 1155:9–11 (Steed Cross 6.22.21).

1537. There is no standard polymorph screen. Each polymorph screen requires a different set of conditions. Trial Tr. at 1155:20–23 (Steed Cross 6.22.21).

1538. Ritonavir, which was sold under the brand name Norvir, was one of first AIDS drugs and was introduced by Abbott Laboratories in the late 1990s. Abbott had made 280 batches of ritonavir, and on the 281st batch, a new polymorph appeared in their production, which they had never seen before, which was more stable and less soluble. Abbott had trouble making the original polymorph after they made the new polymorph. The unexpected creation of a new polymorph was actually due to an impurity issues. The unexpected creation of the new polymorph resulted in Abbott recalling ritonavir and having to reformulate it and get it back on the market, which they were able to do in about six months. This is the only time polymorphism was on the front page of the New York Times, so ritonavir is quite well known in the history of polymorphism. Trial Tr. at 1611:7–19 (Myerson Direct 6.24.21); *see also* PTX-595 at PTX-595_1; PTX-600 at PTX-600_7; PTX-603 at PTX-603_17; PTX-608 at PTX-608_3.

1539. Fieser, Byrn 1994, and Guillory are all general polymorph references that do not mention apremilast, provide experimental data on apremilast, or provide identifying characteristics about apremilast. Trial Tr. at 1210:19–1211:23 (Sacchetti Cross 6.22.21).

1540. Dr. Sacchetti's obviousness theory relies on the present day knowledge that Form A exists, which a POSA would not have known before March 27, 2008 (the priority of date of the '283 Patent), and therefore relies on hindsight. Trial Tr. at 1612:3–7 (Myerson Direct 6.24.21).

1541. Given what a POSA knew regarding the unpredictability of polymorphism, polymorph screening, and the properties of polymorphs, a POSA would not have had a reasonable expectation of successfully obtaining the previously unknown polymorph of apremilast that is now known as Form A. PF ¶¶ 1529–40; Trial Tr. at 1608:20–1609:8, 1611:23–1612:7 (Myerson Direct 6.24.21).

1542. A POSA would not have had a reasonable expectation of success in obtaining Form A on March 27, 2008. Trial Tr. at 1608:20–1609:8, 1611:23–1612:7 (Myerson Direct 6.24.21).

1543. Dr. Sacchetti did not offer any opinions on the ’358 Patent.

1544. Dr. Sacchetti did not offer any invalidity combinations that include Bryn 1995 or Guillory.

XIV. THE ASSERTED CLAIMS OF THE ’541 TITRATION PATENT ARE INFRINGED AND NOT INVALID

A. Person of Ordinary Skill in the Art

1545. The person of ordinary skill in the art for purposes of the ’541 Titration Patent would have been a physician with training and experience in treating psoriasis or psoriatic arthritis, including experience evaluating clinical study results, and with access to someone with expertise in chemistry. Trial Tr. at 1751:19–1752:3 (Alexis Direct 6.25.21).

1546. The evidence presented at trial shows that each of claims 2, 19, and 21 of the ’541 Titration Patent is nonobvious under Amgen’s definition for a person of ordinary skill in the art as well as under Defendants’ proposed definition because the definitions do not materially differ. *See e.g.*, Trial Tr. at 1752:14–17 (Alexis Direct 6.25.21); 831:6–15 (Gilmore Direct 6.21.21).

B. Defendants Infringe the Asserted Claims of the ’541 Titration Patent.

1547. Defendant Zydus has stipulated that the use of its ANDA Products will infringe claims 2, 19, and 21 of the ’541 Titration Patent. ZSF (A2) ¶¶ 14–15 (ECF No. 422).

1548. Defendant Sandoz has stipulated that the use of its ANDA Products will infringe claims 2, 19, and 21 of the ’541 Titration Patent. SSF (A3) ¶¶ 9–12 (ECF No. 422).

C. Defendants Have Failed to Prove by Clear and Convincing Evidence that the Asserted Claims of the ’541 Titration Patent Are Invalid for Obviousness.

1549. Defendants’ only invalidity argument related to the asserted claims of the ’541 Titration Patent is obviousness. Defendants presented one obviousness combination: the ’536 Patent in view of Papp 2012 and Schett 2012. Trial Tr. at 831:20–832:3 (Gilmore Direct 6.21.21) (naming ’536 Patent, Papp 2012, and Schett 2012 “[t]he key references upon which [she] [was] going to rely . . . for [her] invalidity opinion as to the ’541 patent”); *accord id.* at 843:6–11 (Gilmore Direct 6.21.21) (statement of S. Lerner).

1550. The facts relevant to the nonobviousness of each of claims 2, 19, and 21 are the same. Trial Tr. at 1752:24–1753:11 (Alexis Direct 6.25.21).

1551. The effective filing date of the ’541 Titration Patent is August 15, 2014. JTX-13 at JTX-13_1; Trial Tr. at 1752:20–23 (Alexis Direct 6.25.21).

1. State of the art generally regarding dose titration in 2014

1552. Dose “titration” usually refers to the process of starting treatment with a drug typically at a low amount (dose) and increasing the dose of the drug gradually over time until a target dose is reached. Trial Tr. at 1753:23–1754:3 (Alexis Direct 6.25.21).

1553. In 2014, the POSA would have titrated medications according to the conventional approach, which was individualized and feedback-driven, and where the overall titration period would typically span multiple weeks or months. Trial Tr. at 1755:2–1758:10, 1766:9-14, 1769:1–1772:11, 1786:17–1788:2 (Alexis Direct 6.25.21); PTX-413 at PTX-413_19–20; PTX-412 at PTX-412_27; PTX-461 at PTX-461_10; PTX-463 at PTX-463_20; PTX-465 at PTX-465_4–5; PTX-1298 at PTX-1298_39.

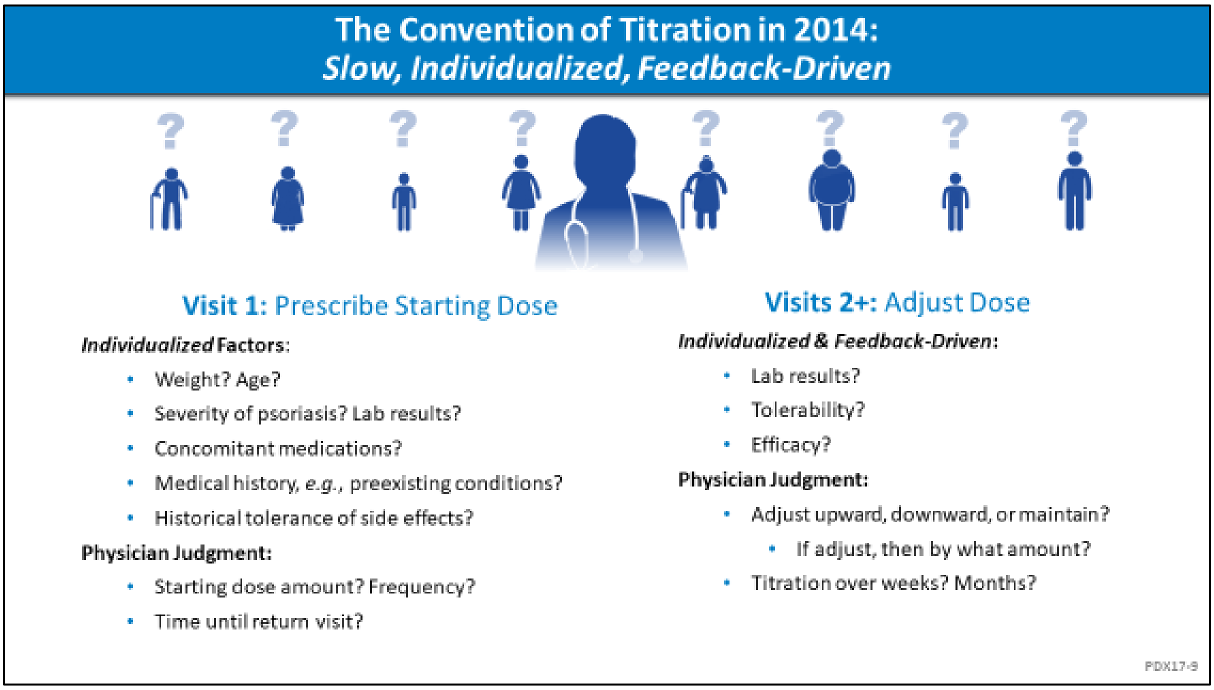
1554. In selecting the appropriate starting dose of a medication to be titrated in 2014 (such as acitretin), the POSA would have considered individualized, patient-specific factors including but not limited to weight, age, severity of disease, medical history and overall health,

concomitant medications, and historical tolerance to any known side effects with the class of drug being titrated. Trial Tr. at 1755:2–1756:13 (Alexis Direct 6.25.21). Knowing all relevant individualized information, the POSA would then decide, based on their sound medical judgment, the starting dose amount, the frequency of dosing, and the amount of time before the patient is to return for a follow-up visit to consider the next dose increase. Trial Tr. at 1755:2–1756:13 (Alexis Direct 6.25.21).

1555. During the first and all subsequent follow-up visits during the titration period in 2014, in order to determine whether to increase, maintain, or decrease the current dose and by how much, the POSA would gather feedback from the patient including but not limited to lab results, the given patient's tolerance for the medication, any safety issues, and the efficacy experienced by the patient. Trial Tr. at 1757:1–16 (Alexis Direct 6.25.21). The decision to change or maintain the dose would be based on the POSA's medical judgment. Trial Tr. at 1757:1–16 (Alexis Direct 6.25.21).

1556. The conventional individualized and feedback-driven titration approach that the POSA would have followed in 2014 would typically span several weeks or months and this was the approach the POSA would have followed to titrate any medication for treating psoriasis in 2014. Trial Tr. at 1757:19-1758:10, 1766:6-17, 1769:1–1771:12 (Alexis Direct 6.25.21); PTX-413 at PTX-413_19–20; PTX-412 at PTX-412_27.

1557. Psoriasis affects a very diverse patient population in terms of, for example, age, gender (approximately a 50/50 distribution between men and women), weight, and preexisting conditions. Trial Tr. at 1756:14–25 (Alexis Direct 6.25.21); *see also* Trial Tr. at 296:13–21 (Alexis Direct 6.15.21) ("When we think of the breakdown of psoriasis between men and women, males and females, it's roughly 50/50.").



1558. The conventional individualized and feedback-driven approach to titration often left patients uncertain, and therefore less confident, about their treatment because they would not know from visit to visit what to expect from the medication in terms of safety, tolerability, or efficacy. Trial Tr. at 1759:5–13 (Alexis Direct 6.25.21).

1559. Every specific example presented at trial of dose titrating a medication other than apremilast followed the conventional individualized and feedback-driven dose titration approach where the titration spans multiple weeks or months. Trial Tr. at 1771:13–1772:11, 1786:17–1788:2 (Alexis Direct 6.25.21); PTX-461 at PTX-461_10; PTX-463 at PTX-463_20; PTX-465 at PTX-465_4–5; PTX-1298 at PTX-1298_39.

Drugs with Lengthy Titration Schedules

Adderall Label	"[D]aily dosage may be raised in increments of 5 mg **at weekly intervals**"
Crestor Label	"Adjustments should be made at **intervals of 4 weeks or more**"
Xanax Label	"Depending on the response, the dose may be increased at **intervals of 3 to 4 days** in increments of no more than 1 mg per day. **Slower titration to the dose levels greater than 4 mg/day may be advisable**."
Paxil Label	"Dose changes should occur at **intervals of at least 1 week**."

Sources: Adderall Label (Rev. 3/2007) [PTX-461_10]; CRESTOR Label (Rev. 06/2010) [PTX-465_4-5]; XANAX Label (Rev. 08/2011) [PTX-463_20]; Paxil Label (Rev. 07/2011) [PTX-1298_39].

PDX17-15

1560. Dr. Alexis's testimony and evidence establishing that the conventional approach to dose titration as of 2014 was individualized, feedback-driven, and would span multiple weeks or months was undisputed at trial. Defendants did not present any testimony or evidence at trial addressing the conventional approach to dose titration in 2014.

2. The unconventional titration schedule claimed in the '541 Titration Patent provides benefits to physicians and patients.

1561. The pre-determined, one-size-fits-all titration schedule claimed in the '541 Titration Patent has a number of benefits over the conventional approach, including improved efficiency and convenience for both doctor and patient. Trial Tr. at 1761:17–1762:15 (Alexis Direct 6.25.21). For the patient, it provides clear directions and removes the uncertainty and need to return to the physician's office or to await further instruction from their physician—an issue with conventional titration that often left patients feeling less confident, and more anxious and uneasy about their treatment. Trial Tr. at 1758:11–1759:13, 1762:6–15 (Alexis Direct 6.25.21). For the physician, it removes the need to evaluate and adjust the patient's dose, eliminating variability. Trial Tr. at 1761:20–1762:5 (Alexis Direct 6.25.21).

1562. The schedule claimed in the ’541 Titration Patent is the approach used with Otezla: the specific dosing schedule claimed in the ’541 Titration Patent is written on the Otezla labeling, and, once apremilast is first prescribed, patients typically take Otezla according to that schedule. Trial Tr. at 1762:16–1764:7 (Alexis Direct 6.25.21). Dr. Alexis explained that his perception was that every one of his colleagues also follows the claimed dosing schedule when using Otezla. Trial Tr. at 1764:11–16 (Alexis Direct 6.25.21).

1563. Dr. Alexis explained that his patients’ experience with the claimed dosing schedule has been very favorable, and the overwhelming majority of his Otezla patients stay on the drug for the long term. Trial Tr. at 1763:17–1764:10, 1764:17–24 (Alexis Direct 6.25.21). His patients appreciate the clear instructions as to what to do on any given day and the fact that they can follow the schedule having an overall very favorable experience. Trial Tr. at 1765:3–14 (Alexis Direct 6.25.21).

3. Defendants’ prior art

a) ’536 Patent

1564. The ’536 Patent was considered by the USPTO examiner during prosecution of the ’541 Titration Patent. JTX-13 at JTX-13_2.

1565. The ’536 Patent teaches that apremilast should be titrated according to the conventional individualized and feedback-driven approach. The ’536 Patent states, “[i]n managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and *increased if necessary* up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, *depending on the patient’s global response*.” JTX-7 at 13:59–63 (emphasis added); *see also* Trial Tr. at 1767:14–1768:7 (Alexis Direct 6.25.21). Defendants’ expert agrees that the ’536 Patent discusses a dosing regimen for apremilast that includes this broad range of doses. Trial Tr. at 833:13–21 (Gilmore Direct 6.21.21).

1566. The POSA would have understood the ’536 Patent’s use of the term, “patient’s global response,” as referring to how the patient is doing clinically—i.e., the patient’s overall response to therapy and encompassing efficacy, safety, and tolerability. Trial Tr. at 1768:8–14 (Alexis Direct 6.25.21).

1567. The ’536 Patent teaches that individualized factors should be taken into account when choosing the appropriate dose of apremilast, including, for example, the patient’s weight, age, sex, severity of condition, or the types of other medicines the patient is taking. *See, e.g.*, JTX-7 at 13:40–49; Trial Tr. at 1766:21–1767:13 (Alexis Direct 6.25.21).

1568. The ’536 Patent teaches that dosing with apremilast may also be impacted by individualized factors like response of the individual patient to apremilast. *See*, *e.g.*, JTX-7 at 13:45–47; Trial Tr. at 1767:14–1768:4 (Alexis Direct 6.25.21).

b) Papp 2012

1569. “Papp 2012” is an article by Dr. Kim Papp and others, entitled “Efficacy of Apremilast in the Treatment of Moderate-to-Severe Psoriasis: A Randomised-Controlled Trial.” DTX-153 at DTX-153_1. Papp 2012 reports on a Phase 2b study of apremilast where patients having moderate to severe plaque psoriasis were titrated to a maintenance dose of either 10, 20, or 30 mg administered twice per day, or placebo. DTX-153 at DTX-153_1; Trial Tr. at 1773:10–23 (Alexis Direct 6.25.21).

1570. Papp 2012 was considered by the USPTO examiner during prosecution of the ’541 Titration Patent. JTX-13 at JTX-13_2.

1571. Papp 2012 was published in the peer-reviewed journal *The Lancet*. DTX-153 at DTX-153_1. Dr. Kim Papp, the first author of Papp 2012, is well-known in the dermatology community and a respected thought-leader in the field. Trial Tr. at 1779:8–21 (Alexis Direct 6.25.21).

1572. Papp 2012 teaches that apremilast was well tolerated and that when adverse events occurred, they appeared over several weeks. It states, "at least half of [adverse] events occurred within 2 weeks of treatment initiation and resolved within a week," indicating that adverse events were recorded for at least three weeks, and perhaps longer. DTX-153 at DTX-153_7.

1573. Papp 2012 does not disclose any particular dose titration schedule. Trial Tr. at 1773:1–6 (Alexis Direct 6.25.21). While Papp 2012 states that dose titration was used in the relevant Phase 2b study, Papp 2012 itself does not contain any details about the dose titration schedule employed in that study. DTX-153 at DTX-153_2. Papp 2012 provides only the following description of that dose titration: "Doses were titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5." DTX-153 at DTX-153_2. There is no other description in Papp 2012 regarding dose titration actually employed in the Phase 2b study. Trial Tr. at 1774:20–1775:1 (Alexis Direct 6.25.21). Thus, the POSA would not have known the precise details of that schedule. Trial Tr. at 1775:2–6 (Alexis Direct 6.25.21). In fact, the one-sentence description of titration in Papp 2012 is so broad that it would be consistent with numerous possible dosing schedules. Trial Tr. at 1775:7–13 (Alexis Direct 6.25.21). The POSA would have understood from Papp 2012 only that doses were titrated to mitigate potential dose dependent adverse events and that all patients arrived at their target dose by no later than the fifth day but possibly sooner. Trial Tr. at 1774:2–19 (Alexis Direct 6.25.21).

1574. Dr. Gilmore's trial testimony confirms that the POSA would not have known the specific titration schedule used in the Phase 2b study based on Papp 2012. Acknowledging "the absence of a detailed description [in Papp 2012]," Trial Tr. at 842:7–10 (Gilmore Direct 6.21.21), but failing to account for the "**by** day 5" language actually found in Papp 2012, DTX-153 at DTX-153_2 (emphasis added), Dr. Gilmore stated without support that the POSA would

"assume that the enrollees would have incremental symmetric or same magnitude increases in dose per day, or per period of time, until the maximum dose is achieved on day 5." Trial Tr. at 839:15–840:5 (Gilmore Direct 6.21.21); *see also* Trial Tr. at 847:15–17 (Gilmore Direct 6.21.21) (discussing "the assumptions of what was written about the dose titration schedule in Papp 2012"). Dr. Gilmore's trial testimony regarding what the POSA would have understood regarding the titration schedule employed in the Phase 2b study of Papp 2012 thus relies on "assum[ption]," Trial Tr. at 839:15–840:5 (Gilmore Direct 6.21.21), in the "absence of" detail, Trial Tr. at 842:7–10 (Gilmore Direct 6.21.21). *See also* Trial Tr. at 840:6–842:10 (Gilmore Direct 6.21.21).

1575. The POSA would not have had any reason to believe that Papp 2012 described a "linear" titration schedule. Dr. Gilmore testified that it was "[h]ighly unlikely that any other type of dosing [*e.g.*, non-linear] would be used in Papp because I would have expected they would then explain that or describe it in more detail." Trial Tr. at 841:23–842:4 (Gilmore Direct 6.21.21); *accord id.* at 842:7–10 (Gilmore Direct 6.21.21). Dr. Gilmore's testimony is inconsistent with Schett 2012, which, like Papp 2012, does not specify any particular titration schedule for the relevant study, *see* DTX-162 at DTX-162_2, yet, the titration schedule that was actually used in the study relevant to Schett 2012 was **<u>non-linear</u>**. Trial Tr. at 857:12–17 (Gilmore Direct 6.21.21).

1576. A different publication, Pathan, would not have filled the gap in the teachings of Papp 2012 regarding the details of the titration schedule used in the relevant Phase 2b study addressed in Papp 2012. Pathan is not cited anywhere in Papp 2012, nor could it have been—it was published several months later, *compare* DTX-157 (Pathan) at DTX-157_1, *with* DTX-153 (Papp 2012) at DTX-153_1. Pathan, meanwhile, cites Papp 2012 only for background on apremilast clinical trials. *See* DTX-157 at DTX-157_1–2. Pathan provides no indication that Pathan's titration schedule had been used in any other study, such as the study described in

Papp 2012. Defendants stated that Dr. Gilmore was not using Pathan as part of the obviousness combinations but only as "background to confirm her understanding of Papp." Trial Tr. at 843:6–15 (Gilmore Direct 6.21.21) (statement of S. Lerner).

1577. The POSA would not have understood the titration schedule described in Pathan to be the same as the schedule used in the psoriasis Phase 2b study of Papp 2012. Trial Tr. at 1840:12–1841:3 (Alexis Cross 6.25.21). The descriptions of titration in Papp 2012 and Pathan are different; whereas Papp 2012 states that "all patients reached the target dose ***by*** day 5," Pathan states that "the maximum dose of 30 mg twice daily was achieved ***on*** day 5." DTX-153 (Papp 2012) at DTX-153_2 (emphasis added); DTX-157 (Pathan) at DTX-157_2 (emphasis added). The fact that the schedule described in Pathan is ***consistent*** with the undisclosed schedule Dr. Gilmore ascribes to Papp 2012 is not probative of whether the POSA in 2014 would have believed the same schedule was used in both clinical studies. *See* Trial Tr. at 1842:22–1843:15 (Alexis Cross 6.25.21) (acknowledging that the schedules are consistent).

1578. The schedule claimed in the '541 Titration Patent is not encompassed by the brief statement in Papp 2012 regarding dose titration at least because the maintenance dose according to the claims of the '541 Titration Patent is reached on day 6, not day 5 (or earlier). *Compare* DTX-153 at DTX-153_2, *with* JTX-13 at 31:3–26.

c) Schett 2012

1579. "Schett 2012" is an article by Georg Schett and others entitled "Oral Apremilast in the Treatment of Active Psoriatic Arthritis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study." DTX-162 at DTX-162_1.

1580. Schett 2012 reports on a Phase 2 study of apremilast where patients having active psoriatic arthritis were titrated to a maintenance dose of either 40 mg QD (once per day) or 20 mg BID (twice per day). DTX-162 at DTX-162_1; Trial Tr. at 1775:19–1776:5 (Alexis Direct 6.25.21).

1581. Schett 2012 was considered by the USPTO examiner during prosecution of the '541 Titration Patent. JTX-13 at JTX-13_2.

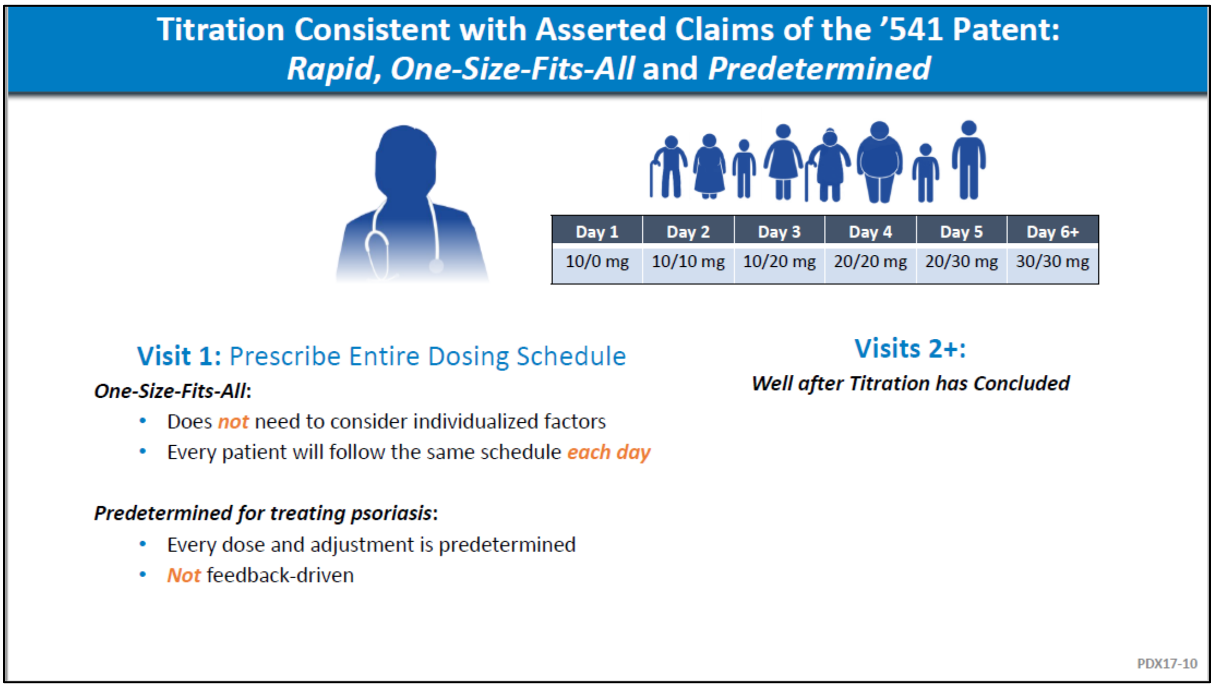
1582. Schett 2012 does not disclose any details about the dose titration schedule employed in the Phase 2b study. DTX-162 at DTX-162_2. Dr. Gilmore's trial testimony confirms that Schett 2012 does not disclose any particular dose titration schedule, as she referenced a separate source for the details of the titration schedule used in the relevant Phase 2 study. Trial Tr. at 850:19–851:3 (Gilmore Direct 6.21.21); *see also* Trial Tr. at 1773:1–6 (Alexis Direct 6.25.21). While Schett 2012 states that dose titration was used in the Phase 2 study it discusses, Schett 2012 provides only the following description of that dose titration: "Dose escalation was implemented during the first 7 days of treatment in an attempt to decrease the likelihood of adverse events (AEs) related to treatment initiation." DTX-162 at DTX-162_2. The POSA would thus have taken away from Schett 2012 only that dose escalation occurred over 7 days and that the reason for titration was to decrease the likelihood of adverse events. Trial Tr. at 1776:9–19 (Alexis Direct 6.25.21).

1583. The schedule claimed in the '541 Titration Patent is not encompassed by the description in Schett 2012 regarding dose titration at least because the maintenance dose according to the claims of the '541 Titration Patent is 30mg BID, not 40mg QD or 20mg BID. *Compare* DTX-162 at DTX-162_2, *with* JTX-13 at 31:3–26.

4. It would not have been obvious to the POSA to use a pre-determined or one-size-fits-all titration schedule.

1584. The apremilast dosing schedule claimed in the '541 Titration Patent is a pre-determined and one-size-fits-all schedule as opposed to an individualized, feedback-driven titration approach. Trial Tr. at 1760:6–1761:1 (Alexis Direct 6.25.21); *see also* Trial Tr. at 907:4–22 (Gilmore Cross 6.21.21). As of the priority date of the '541 Titration Patent, it would not have been obvious to the POSA to use a pre-determined or a one-size-fits-all dose titration schedule for apremilast. Trial Tr. at 1766:6–17 (Alexis Direct 6.25.21). Such an approach to

titration contrasts with the conventional approach as taught in the prior art and used in common clinical practice, where titration involved individualized, feedback-driven dosing. Trial Tr. at 1766:6–17 (Alexis Direct 6.25.21).



1585. It is undisputed that the schedule claimed in the '541 Titration Patent is pre-determined for each individual patient, meaning that the doses and dose increments are not feedback-driven: they are not guided over time by that patient's response to apremilast. Trial Tr. at 1760:6–1761:11 (Alexis Direct 6.25.21); *see also* Trial Tr. at 907:14–19 (Gilmore Cross 6.21.21).

1586. It is undisputed that the method claimed in the '541 Titration Patent recites a specific dosing schedule without including any steps involving evaluation of the patient's response or a physician's judgment in setting or adjusting the dose. *See* Trial Tr. at 1760:6–1761:11 (Alexis Direct 6.25.21); 907:4–22 (Gilmore Cross 6.21.21); JTX-13 at 31:3–26.

1587. It is undisputed that the schedule claimed in the '541 Titration Patent is also one-size-fits-all, meaning that the doses and dose increments are not dependent on individual patient factors such as weight, age, severity of disease, etc.; every patient follows the same

schedule on each day of treatment. Trial Tr. at 1760:6–1761:11 (Alexis Direct 6.25.21); *see also* Trial Tr. at 907:4–22 (Gilmore Cross 6.21.21).

1588. It was not the convention in 2014 to titrate a psoriasis drug according to a pre-determined and one-size-fits-all schedule as of the priority date of the ’541 Titration Patent. Trial Tr. at 1765:15–23, 1769:1–1771:12 (Alexis Direct 6.25.21). Defendants did not offer any contrary evidence, leaving Dr. Alexis’s opinions on this point unrefuted.

1589. Dr. Alexis testified that he is unaware of any other psoriasis therapy available in 2014 that used a pre-determined, one-size-fits-all titration schedule. Trial Tr. at 1765:19–23 (Alexis Direct 6.21.21).

1590. At trial, Defendants did not identify any example of a drug—for the treatment of psoriasis or otherwise—employing a pre-determined or one-size-fits-all dosing schedule prior to apremilast. And with apremilast, Defendants did not identify any example of a pre-determined or one-size-fits-all titration outside of the specific context of conducting a clinical trial.

1591. In the context of the invention of the ’541 Titration Patent, which is directed to the treatment of patients, as well as the parties’ definitions of the POSA, which are each directed to a physician treating patients, Trial Tr. at 1751:14–1752:3 (Alexis Direct 6.25.21); 831:1–831:15 (Gilmore Direct 6.21.21), Defendants failed to adduce any record evidence that the design features peculiar to clinical trials (which are themselves influenced by FDA regulatory approval processes that were not the subject of any qualified expert’s testimony and which are outside the clear boundaries of the parties’ proposed definitions of the POSA) are at all relevant—even where tolerability data are reported for the clinical trials, particularly where those features conflict with conventional physician practice in treating patients.

1592. Acitretin, methotrexate, and cyclosporine were all drugs used to treat psoriasis as of 2014, and the POSA was aware in 2014 that those psoriasis drugs were all titrated

according to the conventional individualized and feedback-driven approach. Trial Tr. at 1755:2–1758:10, 1769:1–1771:4 (Alexis Direct 6.25.21).

1593. Taking acitretin as an example of a drug titrated according to the conventional approach, Dr. Alexis testified how the POSA would have titrated acitretin when treating patients with moderate-to-severe psoriasis as of the priority date of the ’541 Titration Patent. Trial Tr. at 1755:2–1758:10 (Alexis Direct 6.25.21). The POSA would have begun treatment with a first visit with the patient during which he would select an initial dose of medication, as well as an initial frequency of dosing, based on multiple individualized, patient-specific factors such as the patient’s weight, age, severity of disease, disease distribution (i.e., location of plaques on the patient’s body), lab results (e.g., blood tests indicating the patient’s lipid profile and liver function), concomitant medications, pre-existing medical conditions, lifestyle (e.g., whether the patient consumed alcohol), and history with other medications (e.g., history of intolerance or side effects with other drugs and classes of drugs). Trial Tr. at 1755:2–1756:25 (Alexis Direct 6.25.21).

1594. Following the initial visit to treat a patient with acitretin as of the priority date of the ’541 Titration Patent, the POSA would have scheduled multiple follow-up visits with the patient starting approximately four weeks after the first visit and continuing every four weeks for several months subsequent. Trial Tr. at 1757:1–1758:1 (Alexis Direct 6.25.21).

1595. At each follow-up visit when treating a psoriasis patient with acitretin as of the priority date, the POSA would have assessed a variety of factors, including the patient’s clinical response to the treatment, the patient’s tolerance of the treatment, any side effects, and laboratory blood test results. Trial Tr. at 1757:1–18 (Alexis Direct 6.25.21). Based on these factors, the POSA would determine how, if at all, the dose should have been modified. Trial Tr. at 1757:1–18 (Alexis Direct 6.25.21).

1596. As of the priority date of the ’541 Titration Patent, the conventional approach to dose titration with acitretin for moderate to severe psoriasis would take several months. Trial Tr. at 1757:19–1758:1 (Alexis Direct 6.25.21).

1597. The individualized, feedback-driven titration approach described with respect to acitretin is exemplary and consistent with the approaches used with other psoriasis treatments as of the priority date of the ’541 Titration Patent (including, for example, methotrexate and cyclosporine). Trial. Tr. at 1758:2–10, 1769:1–1771:12 (Alexis Direct 6.25.21).

1598. The prescribing information for RHEUMATREX (methotrexate) teaches that “gradual adjust[ment]” should be employed to achieve “optimal clinical response.” PTX-413 at PTX-413_20; *see also* Trial Tr. at 1769:5–1770:3 (Alexis Direct 6.25.21). The POSA would have understood that “gradual adjust[ment]” to achieve “optimal clinical response” as stated in the prescribing information for RHEUMATREX necessarily involves individualizing the dose to fit the patient’s needs and reaction to the drug. Trial Tr. at 1769:5–1770:3 (Alexis Direct 6.25.21); *see also* Trial Tr. at 1758:2–10 (Alexis Direct 6.25.21) (explaining that a similar approach would have been followed across psoriasis therapies).

1599. The prescribing information for NEORAL (cyclosporine) teaches that “[i]f significant improvement has not occurred in patients [in at least four weeks’ time], the patient’s dose should be increased at 2 week intervals. Based on patient response, dose increases . . . should be made . . . .” PTX-412 at PTX-412_27; Trial Tr. at 1770:8–1771:12 (Alexis Direct 6.25.21). The POSA would have understood this to teach feedback-driven, multiple-week dosing where an initial, low dose was held for at least four weeks before increasing based on clinical response. Trial Tr. at 1770:8–1771:12 (Alexis Direct 6.25.21); *see also* Trial Tr. at 1758:2–10 (Alexis Direct 6.25.21) (explaining that a similar approach would have been followed across psoriasis therapies).

1600. The conventional approach of individualized and feedback-driven titration applied outside the context of psoriasis as well. Trial Tr. at 1771:13–1772:8 (Alexis Direct); PTX-461 at PTX-461_10 (ADDERALL label teaching "[r]egardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted according to the therapeutic needs and response of the patient" and raising dose at weekly intervals until "optimal response is obtained"); PTX-463 at PTX-463_20 (XANAX label teaching initiating treatment at "low dose," increasing "[d]epending on the response," "until an acceptable therapeutic response . . . is achieved"); PTX-465 at PTX-465_4–5 (CRESTOR label teaching a range of starting and maintenance doses, variability in dose timing, titration based on patient response and individualized therapy goal, dose adjustment based on analysis of lipid levels "within 2 to 4 weeks" of treatment initiation or titration, and, in certain populations, dose adjustment at "intervals of 4 weeks or more" and maintenance "individualized" dosing "according to the recommended goal of therapy").

1601. The prescribing information documents for RHEUMATREX (PTX-413), NEORAL (PTX-412), ADDERALL (PTX-461), XANAX (PTX-463), and CRESTOR (PTX-465) were all published before August 2014 and are prior art to the '541 Titration Patent. PTX-413 at PTX-413_21; PTX-412 at PTX-412_30; PTX-461 at PTX-461_15; PTX-463 at PTX-463_22; PTX-465 at PTX-465_42; *see also* Trial Tr. at 1769:7–11 (RHEUMATREX), 1770:16–17 (NEORAL), 1772:5–8 (XANAX, ADDERALL, CRESTOR) (Alexis Direct 6.25.21).

1602. The prior art as a whole as of 2014 taught the POSA that *apremilast*, in particular, should be dosed in an individualized, feedback-driven manner. *See* Trial Tr. at 1766:18–1768:25 (Alexis Direct 6.25.21); 904:20–906:17 (Gilmore Cross 6.21.21); JTX-7 at 13:40–49, 13:59–63.

1603. The ’536 Patent, which claims methods of treatment with apremilast, teaches: “The magnitude of a prophylactic or therapeutic dose of a particular active ingredient of the invention in the acute or chronic management of a disease or condition will vary . . . with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The dose, and perhaps the dose frequency, will vary according to the age, body weight, and response of the individual patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors.” JTX-7 at 13:40–49; *see also* Trial Tr. at 1766:21–1767:13 (Alexis Direct 6.25.21); 905:25–906:17 (Gilmore Cross 6.21.21).

1604. The ’536 Patent teaches: “In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and *increased if necessary* up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, *depending on the patient’s global response*.” JTX-7 at 13:59–63 (emphasis added)); *see also, e.g.*, Trial Tr. at 1767:14–1768:4 (Alexis Direct 6.25.21); 904:20–905:21 (Gilmore Cross 6.21.21). The POSA would have understood that “initiated at a lower dose” is a reference to titration. Trial Tr. at 1768:5–7 (Alexis Direct 6.25.21). The POSA would have understood the ’536 Patent’s use of the term, “patient’s global response,” as referring to the overall response to therapy and encapsulating efficacy, safety, and tolerability. Trial Tr. at 1768:8–14 (Alexis Direct 6.25.21). And the POSA would have understood this sentence to teach that the physician may or may not increase the patient’s dose, based on their global response. Trial Tr. at 904:20–905:15 (Gilmore Cross 6.21.21). The POSA could also have understood this sentence to teach that the physician may or may not give a single or divided dose, depending on the patient’s global response. Trial Tr. at 905:16–905:21 (Gilmore Cross 6.21.21).

1605. The ’536 Patent further teaches: “Alternatively, the daily dose is from 0.01 mg/kg to 100 mg/kg.” JTX-7 at 13:63–64; *see also* Trial Tr. at 906:5–17 (Gilmore Cross 6.21.21). The POSA would have understood that to follow such a dosing procedure, the POSA

would need to know the patient's weight, an individualized factor. Trial Tr. at 906:5–17 (Gilmore Cross 6.21.21).

1606. The POSA would not have known from Papp 2012 the dose titration employed in the study on which that reference reports. Trial Tr. at 1773:1–6, 1774:2–1775:13 (Alexis Direct 6.25.21); DTX-153 at DTX-153_2 ("Doses were titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5."). Accordingly, the POSA would not have known whether that schedule was a pre-determined, one-size-fits-all titration schedule. *See, e.g.*, Trial Tr. at 1774:14–19 (Alexis Direct 6.25.21) (stating that Papp 2012 "suggests that there may have been different paths to achieve the target dose").

1607. In light of the other teachings in the art and common practice, the POSA titrating apremilast would have defaulted to the conventional approach of individualized, feedback-driven titration extended over the course of multiple weeks. Trial Tr. at 1755:2–1758:10 (Alexis Direct 6.25.21) (discussing acitretin as an example), 1777:3–10 (explaining that the POSA would have followed the conventional approach if they did not know the details of the Papp 2012 and Schett 2012 titration schedules), 1777:20–1779:2 (explaining that the POSA would have been motivated to follow the conventional approach even having assumed that the POSA were aware of the details of the Papp 2012 and Schett 2012 titration schedules).

5. The POSA would not have been motivated to modify the titration schedule Dr. Gilmore ascribes to Papp 2012.

1608. Even assuming, for the sake of argument, that (1) the POSA had wanted to employ a pre-determined and one-size-fits-all schedule and (2) the POSA was aware of the details of the titration schedule used in the Phase 2b study described in Papp 2012, Defendants failed to establish that the claimed titration schedule would have been obvious to the POSA based on the different titration schedule used in that Phase 2b study. Defendants did not prove

that the POSA would have been motivated to modify the titration approach used in the Phase 2b study reported in Papp 2012. Trial Tr. at 1782:9–16 (Alexis Direct 6.25.21).

1609. Nothing in Papp 2012 would have told the POSA that the titration used in the relevant Phase 2b study proved to be inadequate in mitigating potential adverse events. The Phase 2b study reported in Papp 2012 was a randomized, double-blind, placebo-controlled clinical trial of apremilast in treating moderate to severe plaque psoriasis, which is the gold standard for clinical trials. Trial Tr. at 1781:21–1782:8 (Alexis Direct 6.25.21). Papp 2012 teaches that the titration used in the study favorably mitigated potential adverse events. *See* DTX-153 at DTX-153_1 (apremilast "seems to be efficacious, safe, and tolerable"), _7 ("apremilast 20 mg and 30 mg were associated with significant improvements in quality of life"), _5 ("Headache, nausea, diarrhoea, and vomiting were generally transient and mild or moderate; most did not prompt treatment adjustment or withdrawal. At least half these events occurred within the first 2 weeks of treatment and resolved within a week."), _5 ("All apremilast doses were generally well tolerated, with more than 96% of adverse events rated mild to moderate."), _8 ("Importantly, . . . adverse events commonly associated with phosphodiesterase 4 inhibition (headache, diarrhoea, nausea, vomiting) were generally mild to moderate and transient."); *see also* Trial Tr. at 1779:25–1780:10 (Alexis Direct 6.25.21) ("A POSA reading [page 5 of Papp 2012's statement regarding the general transience and mild to moderate nature of side effects] in the context of the overall publication and study, would be reassured by this statement that apremilast has a tolerability profile that is overall favorable.").

1610. The POSA would have considered Papp 2012 a very credible source of information because Dr. Kim Papp and others of the authors were well-known as leaders in psoriasis research as of 2014, and *The Lancet*, in which Papp 2012 was published, is one of the leading journals in the world. Trial Tr. at 1779:8–21, 1781:1–1782:8 (Alexis Direct 6.25.21). *The Lancet* is not specific to dermatology but is a "very prestigious" journal that addresses

issues relevant to the practice of medicine as a whole, making studies it publishes particularly noteworthy. Trial Tr. at 1781:5–15 (Alexis Direct 6.25.21) (noting *The Lancet* is "part of the broader house of medicine").

1611. Based on the entirety of Papp 2012, including its authorship, its publication in *The Lancet*, its reporting on the gold standard of clinical study data, and its reflection of the success of the titration in terms of mitigating potential adverse events during the study, the POSA would *not* have been motivated to modify the schedule Defendants ascribe to the study reported on in Papp 2012 for tolerability purposes. *See* Trial Tr. at 1782:9–16 (Alexis Direct 6.25.21) (POSA would not have concluded that the alleged Papp 2012 schedule needed improvement for tolerability purposes).

6. It would not have been obvious to the POSA to extend titration by a single day, as opposed to multiple weeks.

1612. Even assuming, for the sake of argument, that (1) the POSA had wanted to employ a pre-determined and one-size-fits-all schedule, (2) the POSA was aware of the details of the titration schedule used in the Phase 2b study described in Papp 2012, and (3) the POSA was motivated to modify that titration schedule—all of which is incorrect—it would not have been obvious to the POSA to extend the titration schedule by a single day as opposed to multiple weeks. Trial Tr. at 1783:2–16 (Alexis Direct 6.25.21).

1613. By convention, the POSA would have used a schedule with a relatively slow titration to 30 mg BID, *i.e.* on the order of several weeks or several months. Trial Tr. at 1757:19–1758:10, 1784:16–21, 1786:17–22 (Alexis Direct 6.25.21).

1614. Papp 2012 would have taught the POSA that a titration schedule spanning three to four weeks or a month would be beneficial to reach a 30 mg BID maintenance dose with apremilast given the observed durations of the tolerability issues. Trial Tr. at 1784:1–15 (Alexis Direct 6.25.21). Papp 2012 teaches that "at least half of [adverse] events occurred within 2 weeks of treatment initiation and resolved within a week." DTX-153 at DTX-153_7. Dr.

Gilmore did not address this language in Papp 2012 during her trial testimony. The POSA would have understood this statement to indicate that adverse events were recorded for at least three weeks in the study reported on in Papp 2012, and perhaps longer. Trial Tr. at 1784:1–15 (Alexis Direct 6.25.21). The POSA would also have understood that the time course of the adverse events observed in Papp 2012 was approximately one month. Trial Tr. at 1784:1–15 (Alexis Direct 6.25.21).

1615. When asked "What would the hope be for the slightly slower dose titration" of the '541 Titration Patent as compared to what Defendants ascribe to the study reported on in Papp 2012, Dr. Gilmore replied: "The hope would be with the smaller dose increases and getting to the goal dose a bit later, that this . . . would help to reduce some of the side effects that we've already talked about that were identified within the first two weeks of treatment within the Papp trial." Trial Tr. at 859:13–21 (Gilmore Direct 6.21.21); *see also* Trial Tr. at 858:1–16 (Gilmore Direct 6.21.21) ("Q. . . . So looking at Papp, if you are still seeing side effects and you are motivated to address them, what would a POSA do? A. A POSA would look to perhaps decrease the magnitude of the dose increases during the initial titration schedule, perhaps start at a lower dose to help ameliorate some of those adverse effects -- events."); Trial Tr. at 862:25–863:7 (Gilmore Direct 6.21.21) (compared to Papp 2012 schedule, '541 Titration Patent "would be more comfortable for the patient").

1616. When asked whether "there was any indication in the prior art before August 2014 that a longer time period would have been obvious to try," Dr. Gilmore cited only the titration schedule used in Schett 2012. Trial Tr. at 863:18–22 (Gilmore Direct 6.21.21).

1617. WO 2011/063102 ("WO '102"), a World International Property Organization patent application published in 2011 and titled "Apremilast for the Treatment of Sarcoidosis," teaches that apremilast titration should occur over the course of at least several weeks, if not more, because it describes an initial dose of 5mg/day and dose escalation (when it occurs)

where the patient spends one week on each dose level. DTX-194 at DTX-194_11 (stating apremilast "may be administered initially in an amount of 5 mg/day and the dose can be escalated every week to 10, 20, 25, 30, 40 and 50 mg/day"); *see also* Trial Tr. at 1785:4–1786:16 (Alexis Direct 6.25.21).

1618. Other psoriasis treatments would have also been titrated over several weeks or months as of the priority date of the '541 Titration Patent, including methotrexate, cyclosporine, and acitretin. Trial Tr. at 1757:19–1758:10 (Alexis Direct 6.25.21); PTX-413 at PTX-413_19–20 (RHEUMATREX label stating: "Dosages in each schedule may be gradually adjusted to achieve optimal clinical response . . . ."); PTX-412 at PTX-412_27 (NEORAL label stating: "If significant clinical improvement has not occurred in patients [in at least four weeks' time], the patient's dose should be increased at 2 week intervals. Based on patient response, dose increases . . . should be made . . . .")).

1619. Outside of treatments for psoriasis, the prescribing information for drugs which are titrated also teach extended, multiple-week titration, and did so as of the priority date of the '541 Titration Patent. Trial Tr. at 1771:24–1772:8, 1786:17–1788:2 (Alexis Direct 6.25.21); PTX-461 at PTX-461_10 (ADDERALL label stating: "[D]aily dosage may be raised in increments of 5 mg at weekly intervals[.]"); PTX-463 at PTX-463_20 (XANAX label stating: "Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable[.]"); PTX-465 at PTX-465_4–5 (CRESTOR label stating: "Adjustments should be made at intervals of 4 weeks or more."); PTX-1298 at PTX-1298_39 (PAXIL label stating: "Dose changes should occur at intervals of at least 1 week.").

1620. Indeed, even Dr. Gilmore agreed that longer titration is understood to be more beneficial in terms of tolerability. When asked "In your view, it's reasonable for a POSA to expect a 28-day titration to make apremilast more tolerable than a five, six, or seven-day

titration, right?" Dr. Gilmore testified: "In my experience, patients have a better shot at continuing with therapy with a longer titration." Trial Tr. at 915:15–19 (Gilmore Cross 6.21.21).

1621. Dr. Gilmore's opinions concerning the duration of titration the POSA would have employed if motivated to depart from the titration used in the Phase 2b clinical study that was the subject of Papp 2012 are explicitly cabined to "clinical trial" design as opposed to the real-world environment actually relevant to the POSA under both parties' definitions in which a physician is treating patients with apremilast. Trial Tr. at 1752:14–17 (Alexis Direct 6.25.21); *see* Trial Tr. at 831:1–831:15 (Gilmore Direct 6.21.21); DTX-153 at DTX-153_7.

1622. Dr. Gilmore was not tendered, much less accepted by the Court, as having the requisite qualifications to give expert testimony about clinical trial design or regulatory processes. Trial Tr. at 814:3–819:24 (Gilmore Voir Dire 6.21.21) (tendered and accepted by the court as an expert "in the field of dermatology and specifically in the treatment of psoriasis"). Yet, without citing any corroborating evidence, Dr. Gilmore testified that the POSA would not employ "a much longer titration schedule than six days" because the side effects "tend to be at the beginning of therapy" and "*in the environment of a clinical trial*, you need to get to your goal dose so that you can start to accumulate data on the treatment." Trial Tr. at 863:8–17 (Gilmore Direct 6.21.21) (emphasis added). Dr. Gilmore also only cited Schett 2012 (*a clinical trial*) as an example of a longer titration period used with apremilast as of the priority date. Trial Tr. at 863:18–22 (Gilmore Direct 6.21.21); *see also* Trial Tr. at 864:13-19 (Gilmore Direct 6.21.21) (opining that there is *nothing* "in the prior art indicating that you would want a longer titration [than seven days] that the POSA would have relied upon") (Gilmore Direct).

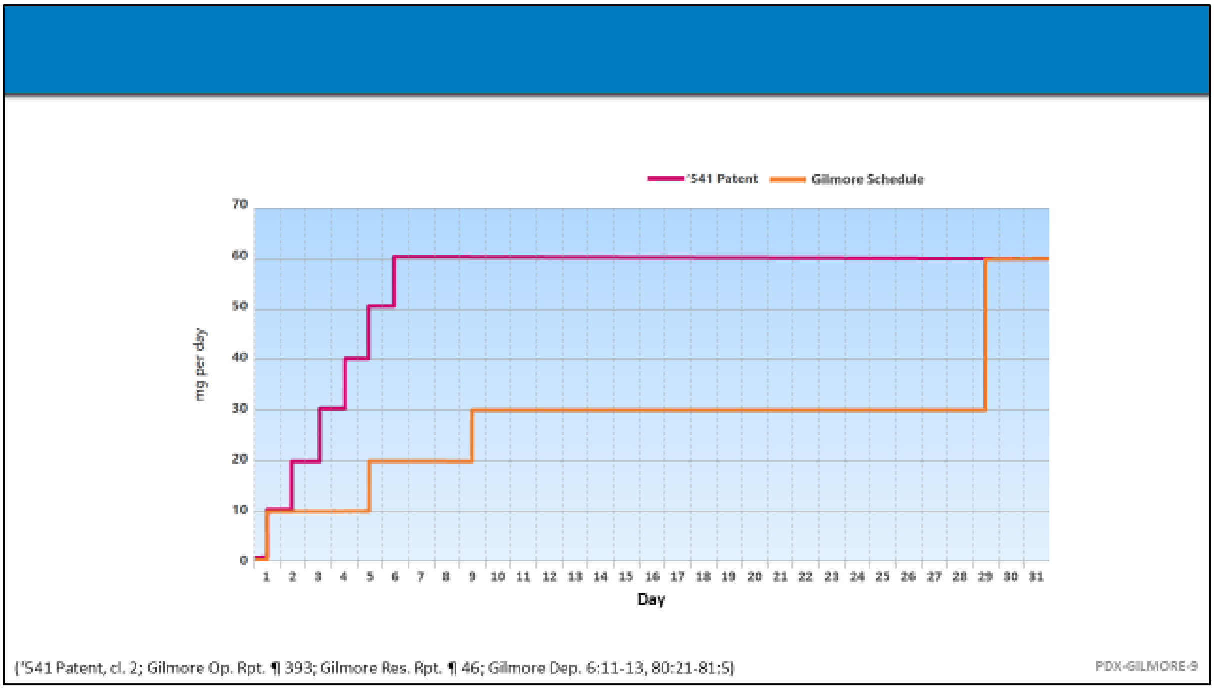
1623. If assuming, for the sake of argument, that the POSA had been motivated to depart from the titration used in the Phase 2b clinical study that was the subject of Papp 2012,

the POSA would have extended the titration schedule by multiple weeks and would not have been constrained by artificial and irrelevant concerns about clinical trial design. First, Dr. Gilmore's testimony to the contrary ignores the most relevant portion of Papp 2012, which states: "at least half of [adverse] events occurred within 2 weeks of treatment initiation and resolved within a week." DTX-153 at DTX-153_7. The POSA would have understood this statement to indicate that adverse events were recorded for at least three weeks in the study reported on in Papp 2012, and perhaps longer, thereby teaching the POSA that the duration of titration would need to be multiple weeks and up to a month to avoid those side effects. Trial Tr. at 1784:1–15 (Alexis Direct 6.25.21). Dr. Gilmore's testimony also ignores the teachings of WO '102 and the convention of how drugs for psoriasis (e.g., acitretin, methotrexate, and cyclosporine) and other disorders for which titration was recommended (e.g., Adderall, Paxil, Crestor, and Xanax) were titrated as of the priority date—i.e., over multiple weeks or months. Trial Tr. at 1757:19–1758:10 (Alexis Direct 6.25.21) (discussing acitretin, methotrexate, and cyclosporine), 1785:18–1786:16 (discussing WO '102), 1786:17–1788:2 (discussing Adderall, Xanax, Crestor, and Paxil); DTX-194 at DTX-194_11; PTX-413 at PTX-413_19–20; PTX-412 at PTX-412_27; PTX-461 at PTX-461_10; PTX-463 at PTX-463_20; PTX-465 at PTX-465_4–5; PTX-1298 at PTX-1298_39.

1624. The fact that Dr. Gilmore never explained by what point in time one would need to "start to accumulate data," why one could not "accumulate data" while titrating the dose over multiple weeks, or whether her testimony was rooted in any FDA or other regulatory requirement is not surprising given she was never accepted by the Court to give expert testimony concerning clinical trial design or regulatory processes. A lack of both expertise and supporting evidence also explains Dr. Gilmore's equivocal concluding testimony on this point, stating only that "extending [titration] a significant amount of time **<u>may not be</u>** a realistic exercise." Trial Tr. at 863:16–17 (Gilmore Direct 6.21.21) (emphasis added).

1625. Furthermore, both sides' POSA definitions with respect to the claims of the '541 Titration Patent are directed to a physician treating patients—not a person seeking to, let alone qualified to, design clinical trials or engage in regulatory processes. Trial Tr. at 1751:21–1752:3 (Alexis Direct 6.25.21); 831:1–831:15 (Gilmore Direct 6.21.21). Accordingly, Dr. Gilmore's improper and unsupported testimony about the "clinical trial environment" is completely irrelevant to evaluating what ***the POSA*** would or would not have been motivated to do in light of the prior art of record. Dr. Gilmore's improper, irrelevant, and equivocal testimony concerning the clinical trial environment carries no weight.

1626. Dr. Gilmore's own actions also undermine her opinions regarding the length of titration the POSA would have employed to address tolerability issues with apremilast. Dr. Gilmore opined that the POSA would have selected the titration schedule claimed in the '541 Titration Patent if trying to overcome tolerability issues. *E.g.*, Trial Tr. at 919:15–21 (Gilmore Direct 6.21.21). When Dr. Gilmore herself was trying to solve tolerability issues associated with apremilast, however, she extended the labeled titration by ***23 days***, for a total of ***29 days*** of titration to reach a 30mg BID maintenance dose. Trial Tr. at 919:11–25 (Gilmore Cross 6.21.21); 947:17–948:13 (Gilmore Redirect 6.21.21) (noting, *inter alia*, that Dr. Gilmore began extending titration around 2017). At trial, Dr. Gilmore could not recall even considering extending the titration by a single day. Trial Tr. at 914:21–24 (Gilmore Cross 6.21.21).



1627. Dr. Gilmore's practice of extending titration of apremilast by weeks comports not only with the teachings in Papp 2012, but also with the practices of other Otezla prescribers. With the objective of further improving tolerability, physicians (including "Key Opinion Leaders") on several Celgene advisory boards reported extending apremilast titration by providing two or three titration packs per patient, thereby extending titration by a week or more. JTX-100 at JTX-100_26; JTX-98 at JTX-98_4, JTX-98_11; *see also* Trial Tr. at 1860:17–22, 1861:5–9, 1863:5–1864:2 (Alexis Cross 6.25.21). Some physicians specifically suggested that patients double the length of time to achieve the full 30mg BID dose, i.e., from 6 to 12 days. JTX-100 at JTX-100_26.

1628. Dr. Gilmore also testified that apremilast's efficacy imposed no constraint on the POSA adopting a multi-week titration schedule. Dr. Gilmore explained at trial that apremilast "is a medication that has a -- slower onset of action. It would take **months** to -- to determine how efficacious something was." Trial Tr. at 912:16-18 (Gilmore Cross 6.21.21) (emphasis added); *see also* Trial Tr. at 915:15–916:1 (Gilmore Cross 6.21.21). She further admitted that the POSA would have understood in 2014 that apremilast takes several months to show efficacy. Trial Tr. at 916:2–4 (Gilmore Cross 6.21.21); *see also* Trial Tr. at 1866:7–18

(Alexis Redirect 6.25.21) (describing data in the prior art showing that most patients respond to apremilast over a period of weeks and months after the start of treatment). Because the POSA knew in 2014 that efficacy is not a concern in the first several months of apremilast therapy, the POSA had no motivation to limit themselves to titration schedules of one week or less.

7. It would not have been obvious to the POSA to arrive at the claimed schedule from among many, many possibilities.

1629. The POSA would not have arrived at the dosing schedule claimed in the '541 Titration Patent through what Dr. Gilmore describes as "routine optimization," Trial Tr. at 858:5–20, 859:13–25, 861:10–17 (Gilmore Direct 6.21.21); 909:19–23 (Gilmore Cross 6.21.21), of the dosing schedule Dr. Gilmore ascribes to Papp 2012. Trial Tr. at 1788:11–16 (Alexis Direct 6.25.21). It would not have been obvious for the POSA to arrive at the claimed schedule in particular from among many, many possibilities. Trial Tr. at 1788:19–23 (Alexis Direct 6.25.21). The number of possibilities available to the POSA would have been "enormous." Trial Tr. at 1788:24–1789:5, 1794:14–17 (Alexis Direct 6.25.21).

1630. The POSA developing a new dose titration schedule would have needed to consider the many variables that must be decided upon to arrive at a particular dosing schedule. Trial Tr. at 1789:6–1790:19 (Alexis Direct 6.25.21). Such variables include, for example: time to reach maintenance dose; amount of the initial dose; amount of the maintenance dose; amount of each dose increment; morning and/or afternoon dosing; number of dose increments; frequency of dosing; time between increments; linear (consistent increases over time) or non-

linear. Trial Tr. at 1789:6–1790:19 (Alexis Direct 6.25.21).

Exemplary Variables in Designing a Dose Titration Schedule

Variables	Selection
Length of titration	?
Amount of initial dose	?
Amount of maintenance dose	?
Increment amounts	?
AM or PM dosing, or both	?
Number of increments	?
Frequency of dosing	?
Duration between increments	?
Linearity or non-linearity of increase (amounts? intervals?)	?

PDX17-17

1631. Each of these variables would have presented the POSA with multiple options. Taking the "amount of the initial dose" as an example, the POSA could have considered any of a range of apremilast doses, such as 1 mg, 5 mg, 10 mg, or others. Trial Tr. at 1789:14–24, 1791:8–22 (Alexis Direct 6.25.21). Dr. Gilmore contradicted her assertion that the '536 Patent would "make it obvious . . . to start at a 10-milligram dose in a titration schedule." *See* Trial Tr. at 857:22–25 (Gilmore Direct 6.21.21). The '536 Patent teaches doses in various amounts. *See, e.g.*, JTX-7 at 13:49–64 ("5 mg, 10mg, 15 mg, 20mg, 25 mg, 50mg, or 100 mg dosage forms"), 13:59–63 ("In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg . . . ."). Dr. Gilmore admitted that nothing in the '536 Patent identifies 10 mg as being preferable over the other potential starting doses of apremilast the '536 Patent identifies. Trial Tr. at 834:7-10 (Gilmore Direct 6.21.21). Thus, the POSA would not have been limited to starting doses of 10 mg on the first day. Trial Tr. at 1791:8–22 (Alexis Direct 6.25.21).

1632. The POSA also would have needed to decide whether the first dose would be a single dose (e.g., morning or afternoon) or a divided dose (e.g., morning and afternoon); and if a single dose, the time of day of that single dose. Trial Tr. at 1791:14–22 (Alexis Direct 6.25.21). The dosing schedule claimed in the ’541 Titration Patent, for example, requires that 10 mg apremilast be administered as a single dose in the morning of the first day of treatment. *E.g.*, JTX-13 at 31:7–13 (cl. 2).

1633. Defendants have failed to offer any evidence that the prior art taught starting titration with a dose of 10 mg apremilast *in the morning* on the first day (with no dose in the afternoon of that first day). At best, Dr. Gilmore opined that the prior art—in particular, the schedule she ascribes to Schett 2012—taught a 10 mg daily dose “QD” (once daily), *without regard to the time of day*. *See, e.g.*, Trial Tr. at 857:18–21 (Gilmore Direct 6.21.21) (“This teaches us that 10 milligrams once daily can be used as part of a titration schedule.”).

1634. Had the POSA looked to the titration schedule Dr. Gilmore ascribes to Schett 2012 for guidance on how to modify the schedule Dr. Gilmore ascribes to Papp 2012, the POSA would not have arrived at the claimed invention. Trial Tr. at 1793:16–20 (Alexis Direct 6.25.21).

1635. Despite some possible overlap on the first day between the titration schedule Dr. Gilmore ascribes to Schett 2012 (by reference to NCT ’092) and the schedule claimed in the ’541 Titration Patent, the schedules differ in many other respects. Examples of differences between the titration schedule Dr. Gilmore ascribes to Schett 2012 (by reference to NCT ’092) and the schedule claimed in the ’541 Titration Patent include:

- the schedules reach different maintenance doses (40 mg per day in Schett 2012 versus 60 mg per day in the ’541 Titration Patent;
- the schedules differ from one another on ***every single day*** (with the exception of possibly day 1 where both schedules have 10 mg on the first day as the total daily dose but it is not clear what time of day apremilast is dosed according to Schett

2012, whereas the schedule claimed in the ’541 Titration Patent specifies that the first dose be administered in the morning);

- the schedules meet the maintenance dose on different days (day 8 in Schett 2012 versus day 6 in the ’541 Titration Patent);
- the Schett 2012 schedule includes 2 daily increments (daily dose increases from day 3 to 4 and from day 7 to 8), whereas the ’541 Titration Patent schedule includes 5 daily dose increments (the daily dose increases each day);
- the Schett 2012 schedule has increments that are separated by three- and four-day intervals, whereas the ’541 Titration Patent schedule has increments that are separated consistently by one-day intervals; and
- the Schett 2012 schedule has non-linear increments of both 10 mg and 20 mg and at unequal intervals, whereas the ’541 Titration Patent schedule has linear increments of 10 mg that are consistently 10 mg at equal intervals;

Trial Tr. at 1792:2–1793:15 (Alexis Direct 6.25.21); *see also* Trial Tr. at 857:10–17 (Gilmore Direct 6.21.21) (discussing dose titration described in NCT ’092); DTX-092 at DTX-092_3 (“To ameliorate the dose dependent adverse events of CC-10004 (headache and GI disturbances) there will be dose titration of 10mg QD (or placebo) for days 1-3 followed by 20mg QD (or placebo) days 4 to 7 in the first week of dosing.”); JTX-13 at 31:3–26.

1636. The POSA would not have had any reason to adopt only the first day of the titration schedule Dr. Gilmore ascribes to Schett 2012 and ignore the other aspects of that schedule. Trial Tr. at 1794:1–7 (Alexis Direct 6.25.21). Dr. Gilmore offered no explanation as to why or how the POSA would have adopted only the first day of the schedule Defendants ascribe to Schett 2012 (10mg) but not the other aspects of the schedule.

1637. Dr. Gilmore admitted that there are at least several “major” differences between the schedule claimed in the ’541 Titration Patent and the schedule she ascribes to the 30 mg BID arm of the Phase 2b study described in Papp 2012:

- the schedules have different starting doses;

- the schedules have different dose increments; and
- the schedules reach the 30 mg BID maintenance dose on different days.

Trial Tr. at 860:12–861:9 (Gilmore Cross 6.21.21).

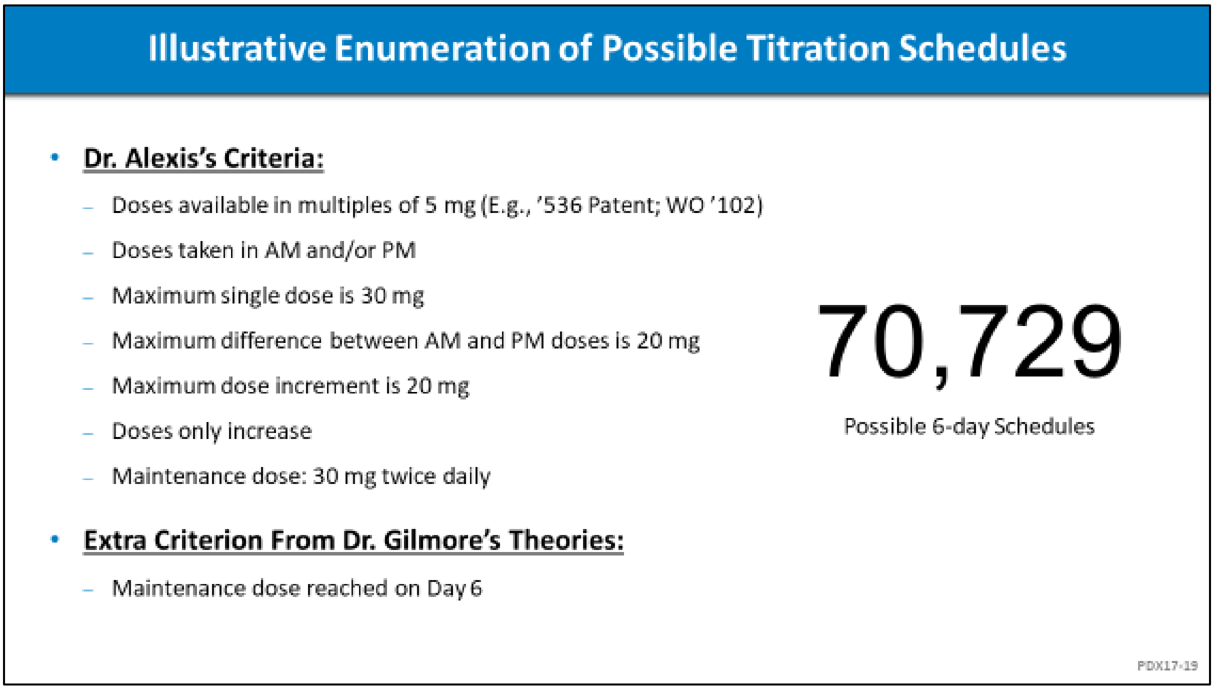
1638. Dr. Gilmore failed to show why or how the POSA would have bridged all of the differences between the schedule she ascribes to Papp 2012 and the schedule claimed in the ’541 Titration Patent.

1639. Just to illustrate some of the numbers of possible dose titration schedules for apremilast, Dr. Alexis designed a set of parameters, or criteria, for titration schedule variables that would be reasonable for the POSA to consider based on the prior art and the POSA’s knowledge. Trial Tr. at 1794:20–1795:4 (Alexis Direct 6.25.21). Dr. Alexis then worked in collaboration with a biostatistician, Dr. Ronald Thisted, to calculate the numbers of different possible permutations of titration schedules that meet Dr. Alexis’s criteria. Trial Tr. at 1797:16–24 (Alexis Direct 6.25.21).

1640. One example of a reasonable criterion is that the POSA would have understood that apremilast could be dosed in increments of 5 mg. For example, the ’536 Patent discloses “5 mg, 10mg, 15 mg, 20mg, 25 mg, 50mg, or 100 mg dosage forms.” *See* JTX-7 at 13:49–64. Another apremilast reference also discloses dosage forms in increments of 5 mg. DTX-194 at DTX-194_11 (WO ’102 describing “apremilast for the treatment of sarcoidosis” and stating that apremilast “may be administered initially in an amount of 5 mg/day and the dose can be escalated every week to 10, 20, 25, 30, 40 and 50 mg/day”). Dosage forms in increments of 5 mg are common with drugs other than apremilast, as well. Trial Tr. at 1795:5–12 (Alexis Direct 6.25.21). Indeed, Dr. Gilmore admitted at trial that the POSA would have had options beyond 10 mg, 20 mg, and 30 mg dosage forms. *See* Trial Tr. at 926:18–25 (Gilmore Cross 6.21.21).

1641. Others of Dr. Alexis's illustrative criteria include: morning and/or evening doses, maximum single dose is 30 mg, maximum difference between morning and afternoon doses is 20 mg, maximum dose increment is 20 mg, doses only increase, and the maintenance dose is 30 mg twice per day. Trial Tr. at 1795:5–1796:14 (Alexis Direct 6.25.21). For this illustrative exercise, Dr. Alexis also specified that the maintenance dose would be reached precisely on day 6, taking as an assumption, for the sake demonstration only, Dr. Gilmore's meritless assertion that the POSA would have arrived at a 6-day titration schedule. Trial Tr. at 1796:15–1797:15 (Alexis Direct 6.25.21).

1642. Even when taking as an assumption Dr. Gilmore's assertion that the maintenance dose would be reached on day 6—an assertion with which Dr. Alexis disagrees—there are over 70,000 different possibilities for titration schedules that meet each of Dr. Alexis's reasonable criteria. Trial Tr. at 1796:15–1797:15 (Alexis Direct 6.25.21); 1851:5–18 (Alexis Cross 6.25.21). The POSA in 2014 would not have had any basis to determine which of the more-than 70,000 possibilities would be optimized according to tolerability. Trial Tr. at 1799:2–6 (Alexis Direct 6.25.21).



1643. In addition, the number of possibilities for different titration schedules would increase considerably to a very large number if the POSA were to accept that the maintenance dose could be reached any time between day 6 and day 29. Trial Tr. at 1798:15–1799:1 (Alexis Direct 6.25.21). Dr. Gilmore testified that a 29-day titration schedule to reach 30 mg BID of apremilast (namely, the 29-day titration schedule she chose to adopt when departing from the claimed titration schedule) is a "reasonable schedule for dosing apremilast." Trial Tr. at 920:14–17 (Gilmore Cross 6.21.21).

1644. Even when assuming nearly ***all*** of the limitations of the claimed titration schedul*e*—e.g., a 6-day titration (inconsistent with any prior art reference and Dr. Gilmore's own titration practices), dosage forms limited to 10, 20, and 30 mg (inconsistent with the teachings of the '536 Patent and WO '102), and dose increments at equal intervals over time (inconsistent with the titration schedule Dr. Gilmore ascribes to Schett 2012), there are ***still 18*** different possibilities, only one of which is the claimed dosing schedule. Trial Tr. at 1856:24–1867:10 (Alexis Cross 6.25.21). In any event, the POSA would not have had any motivation to limit themselves so that they essentially had nearly every limitation of the claimed titration in hand in order to reduce the possibilities to 18 schedules. Trial Tr. at 1867:11–1868:21 (Alexis Redirect 6.25.21).

1645. Even assuming the POSA somehow had 18 schedules to consider—and the POSA would have had many, many more given reasonable parameters—the POSA would have needed to test out each of the different schedules in order to determine which of them was the best in terms of tolerability. Trial Tr. at 1868:22–1869:3 (Alexis Redirect 6.25.21). In 2014 it would not have been a routine matter to optimize a predetermined or one-size-fits-all titration schedule for apremilast. Trial Tr. at 1799:2–14 (Alexis Direct 6.25.21). The POSA in 2014 would also not have had a reasonable expectation of success that any one of the possible

titration schedules would be an optimized titration schedule. Trial Tr. at 1799:15–18 (Alexis Direct 6.25.21).

8. Defendants' assertions regarding the absence of "unexpected results" are irrelevant.

1646. The testimony of Defendants' biostatistician, Dr. Scharfstein, regarding unexpected results is irrelevant. Dr. Scharfstein opined that he disagreed with Celgene's attorney analysis presented during prosecution of the '541 Titration Patent regarding the presence of unexpected results, a type of objective indicium of nonobviousness. *See* Trial Tr. at 951:4–993:24 (Scharfstein Direct 6.21.21). That testimony has no bearing on this case because Amgen did not assert unexpected results at trial. Regardless of whether Dr. Scharfstein's analysis regarding the particulars of the unexpected results arguments made during prosecution is correct, even the absence of unexpected results could not weigh in favor of obviousness.

1647. There is also no basis in the record to conclude that the USPTO examiner allowed the asserted claims of the '541 Titration Patent because of unexpected results. Neither Dr. Scharfstein, nor any other of Defendants' experts opined that unexpected results is the reason why the USPTO allowed the '541 Titration Patent. *See, e.g.*, Trial Tr. at 994:4–25 (Scharfstein Cross 6.21.21). Indeed, Dr. Scharfstein admitted that he is not an expert in patent law or in patent office practice and procedure. Trial Tr. at 994:11–15, 995:1–10 (Scharfstein Cross 6.21.21).

1648. Defendants' attorney's assertion that unexpected results is "what got [Celgene] the patent ultimately," Trial Tr. at 71:4–6 (Lombardi Opening Statement 6.14.21), is not only unsupported by any evidence, but it is also refuted by the patent examiner's 2018 explanation for why she allowed the patent. In her 2018 explanation of the "REASONS FOR ALLOWANCE," the examiner did not mention unexpected results. JTX-24_1230–31; *see also* Trial Tr. at 999:20–1000:12 (Scharfstein Cross 6.21.21).

1649. Defendants' position is also refuted by other developments during prosecution. Contrary to suggesting that arguments about unexpected results persuaded her, the examiner explicitly explained that those arguments—among others—became "***moot***" in light of new rejections. After receiving Celgene's arguments concerning, among other things, unexpected results, the examiner stated on October 23, 2017: "Applicants' arguments, filed on May 19, 2017, have been fully considered ***but they are moot*** in view of new grounds of rejection. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn." JTX-24 at JTX-24_1081 (date), JTX-24_1083 (quote) (emphasis added).

1650. Even assuming "moot[ed]" arguments could have played a role in the ultimate allowance, there is nothing in the record indicating that it was the arguments about unexpected results—rather than the other, independent arguments Celgene advanced—that secured the patent. In May 2017, in response to an examiner rejection for obviousness over the combination of the '536 Patent, Papp 2012, and Schett 2012, Celgene advanced several arguments. *See, e.g.*, JTX-24 at JTX-24_804 (date), JTX-24_798–803 (argument). The first of Celgene's arguments was a response to the examiner's asserted prima facie case, having nothing to do with unexpected results. *See, e.g.*, JTX-24 at JTX-24_800 ("As none of the '536 Patent, Schett, or Papp, alone or combination, contain a teaching, suggestion, or motivation of a titration schedule that increases by 10 mg/day to a dosage of 30 mg BID as recited in instant claims, Applicant respectfully submits that the Office has improperly used hindsight reconstruction to find the present claims obvious."); Trial Tr. at 998:1–17 (Scharfstein Cross 6.21.21). The applicant's secondary argument, which related to unexpected results, was made conditionally: "even assuming, *arguendo*, that a case of *prima facie* case [sic] of obviousness has been established by the Office, with which Applicant disagrees, the evidence of unexpected results attached hereto rebuts any *prima facie* case of obviousness." JTX-24 at JTX-24_800; Trial Tr. at 998:18–24 (Scharfstein Cross 6.21.21).

1651. Dr. Scharfstein's specific testimony regarding statistical significance is likewise irrelevant. Dr. Scharfstein made clear that his opinion was based on a misinterpretation of a statement in the file history of an unrelated patent, U.S. Patent No. 9,872,854 ("'854 Patent File History"). Dr. Scharfstein testified that in a response to an office action in the '854 Patent file history, the Applicant was "talking about the Papp and the Kavanaugh studies," and he testified that it was not "true" that "when you look at the treatment effects, that is the 13.1 percent and the 17 percent, . . . these results are statistically significant." Trial Tr. at 980:2–980:16 (Scharfstein Direct 6.21.21). But Dr. Scharfstein's testimony appears to be based on a misreading of the file history, which actually states, "[g]iven that there was ***168 patients*** in the relevant cohort (30 mg BID), these results are statistically significant." JTX-23 at JTX-23_700 (emphasis added). The reference to "168 patients" can only be referring to Kavanaugh (which described a study involving 168 patients in the 30 mg BID treatment arm) because Papp 2012 had only 88 patients in its 30 mg BID treatment arm. *See* Trial Tr. 1001:7–1002:4 (Scharfstein Cross 6.21.21); JTX-221 at JTX-221_6 ("n=168"); DTX-153 at DTX-153_6 ("n=88"). Thus, there is no reason to conclude that the Applicant was "talking about the ***Papp and*** Kavanaugh studies" with regard to statistical significance, as Dr. Scharfstein erroneously assumed. Dr. Scharfstein appears not to have considered, for example, whether there was a statistically significant difference in adverse events rates between the active and placebo arms of just Kavanaugh. Even assuming the unrelated patent file history were somehow relevant to the disputed issues in this case involving the '541 Titration Patent, which it is not, nothing in that file history suggests that the asserted claims of the '541 Titration Patent would have been obvious.

Date: July 8, 2021

s/Charles H. Chevalier
Charles H. Chevalier
J. Brugh Lower
Christine A. Gaddis
Rachel S. Johnston
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102-5310
(973) 596-4611

Attorneys for Plaintiff Amgen Inc.

OF COUNSEL:

George F. Pappas
Jeffrey B. Elikan
Kevin B. Collins
Michael N. Kennedy
Jay Alexander
Priscilla Dodson
Alexander Trzeciak
Philip S. May
Antonio J. Carvalho
Joseph Hykan
Priscilla N.A. Nyankson
Daniel H. Lee
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street NW
Washington, DC 20001-4956
(202) 662-6000

Alexa Hansen
David S. Denuyl
COVINGTON & BURLING LLP
Salesforce Tower
415 Mission Street, Ste. 5400
San Francisco, California 94105
Tel: (415) 591-7035

Robert Zhou
COVINGTON & BURLING LLP
3000 El Camino Real
Palo Alto, California 94306
(650) 632-4700

Steven J. Horowitz
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, Illinois 60603
(312) 853-7000

Sue Wang
SIDLEY AUSTIN LLP
555 California Street, Suite 2000
San Francisco, California 94104
(415) 772-1200

Wendy A. Whiteford
Eric M. Agovino
C. Nichole Gifford
Dennis Smith
Gregory Bonifield
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1789

Attorneys for Plaintiff Amgen Inc.